20th Annual Meeting, American College of Chest Physicians
San Francisco, California, June 17 - 20, 1954

VOLUME XXV NUMBER 5

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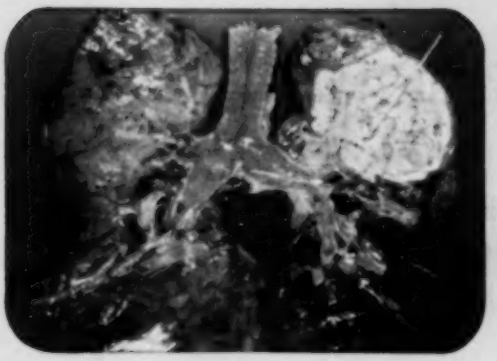

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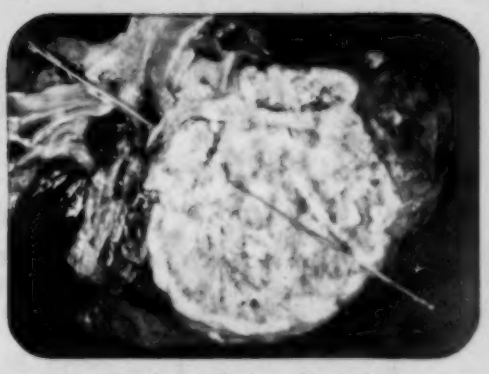

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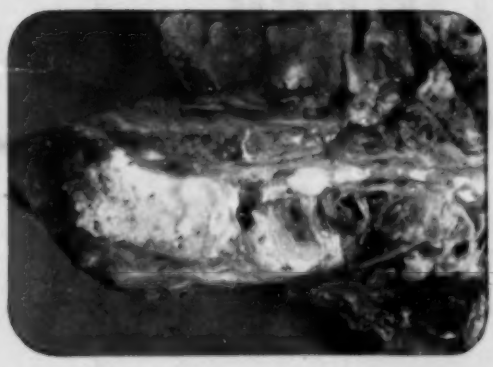

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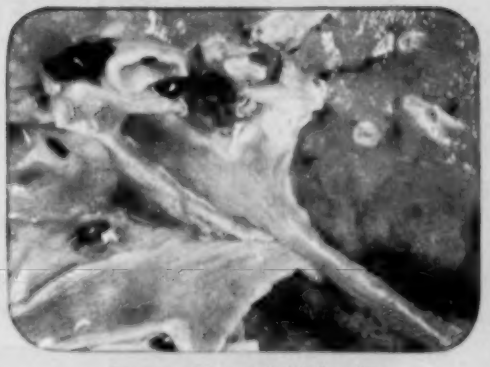

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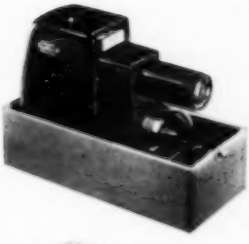

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OFFICIAL PUBLICATION

OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

VOLUME XXV MAY 1954 NUMBER 5

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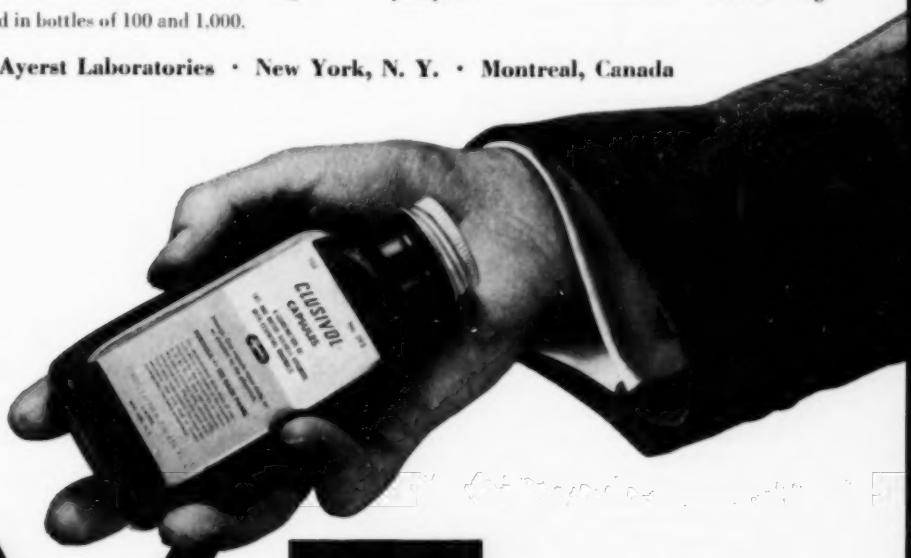

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1. Gordon, B., "The Mechanism and Use of Abdominal Supports and the Treatment of Pulmonary Diseases". Am. J. Med. Sc. 187:692, 1934.

2. Barach, A.L., Bicherman, H.A., and Beck, G. "Advances in the Treatment of Non-Tuberculous Pulmonary Diseases." Bull. N. Y. Acad. Med. 28:353, 1952.

3. Barach, A.L. and Beck, G. "The Value of Mechanical Methods of Aiding Respiratory Function." To be published.

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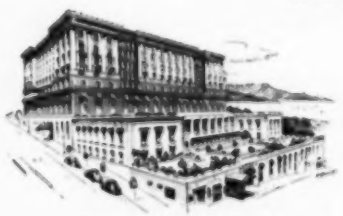

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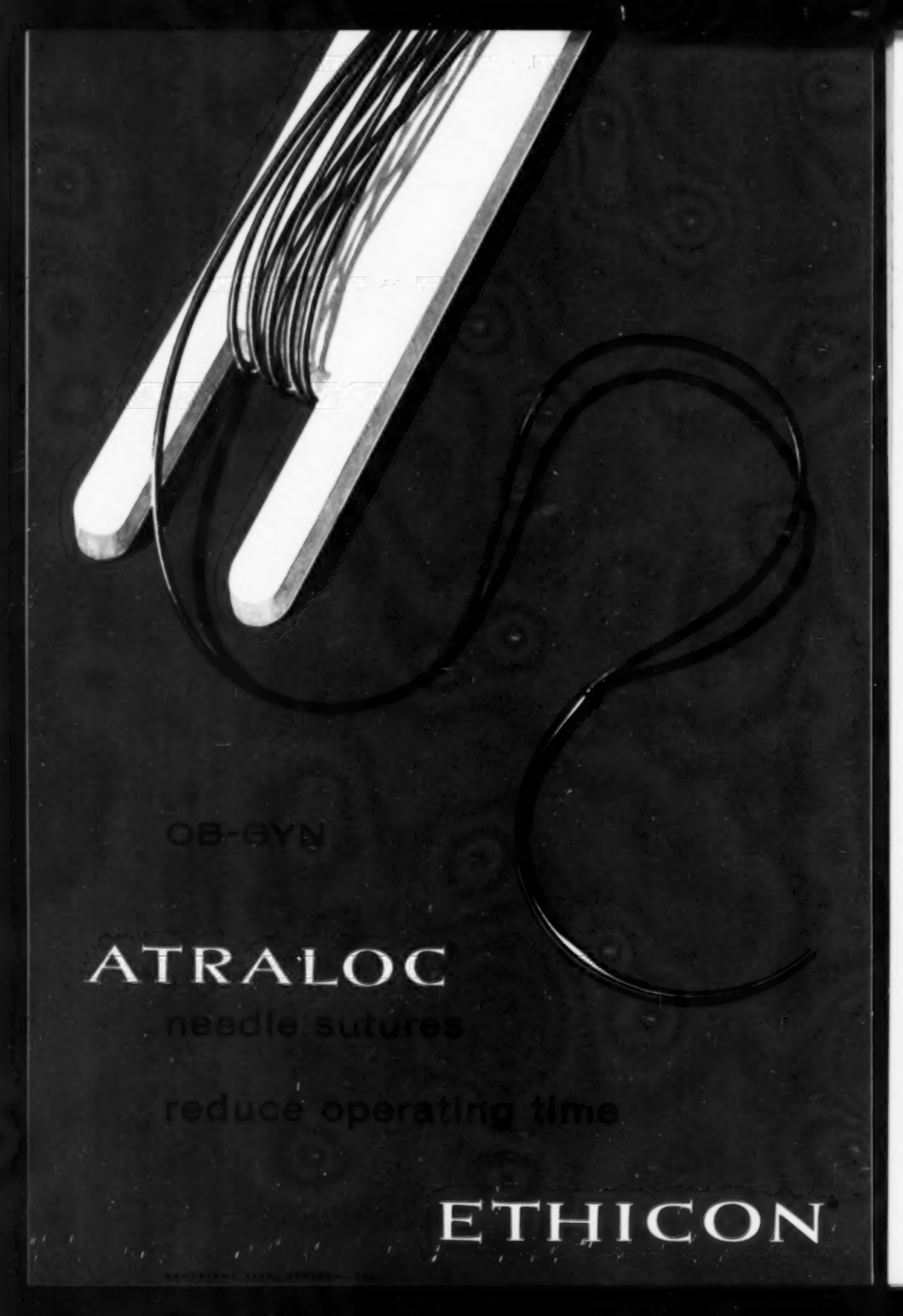
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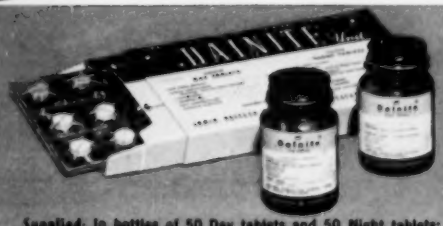

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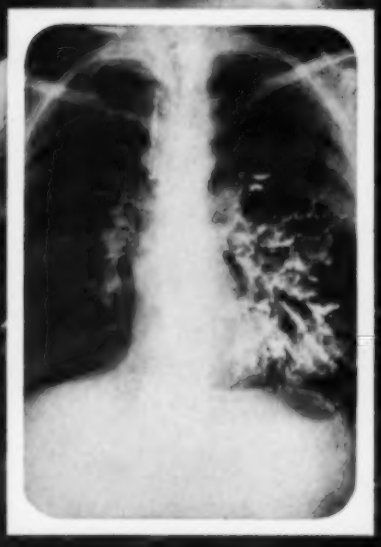

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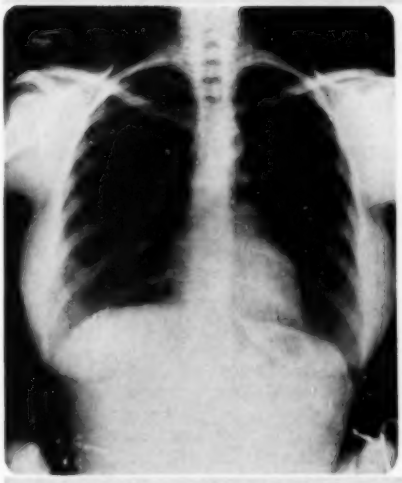
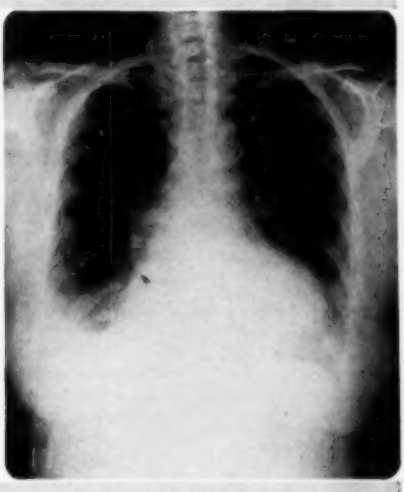


Patient A—Normal heart



Patient B—Cardiac hypertrophy in congestive failure

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DISEASES *of the* CHEST

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A Symposium on Electrocardiography

INTRODUCTION

ALDO A. LUISADA, M.D., F.C.C.P.
Chicago, Illinois

Electrocardiography had a rapid development and is now based on a standardized technique. The following symposium had the purpose of discussing several aspects which are still controversial.

The symposium was presented at the Hotel New Yorker in New York City during the 19th Annual Meeting of the American College of Chest Physicians on May 29, 1953. Dr. John Briggs, of Minneapolis, was the moderator.

The Normal Electrocardiogram*

LOUIS WOLFF, M.D.
Boston, Massachusetts

The normal electrocardiogram varies within remarkably wide limits. It may be defined as the "average type curve" obtained under basal conditions in most individuals of all age groups who have no heart disease, and are in good health. Nevertheless, normal tracings may be observed in the presence of serious heart disease, and tracings which are obviously abnormal are not infrequently noted in individuals in whom it is impossible to demonstrate structual heart disease by all known methods of examination. Right and left bundle branch block are good examples of such abnormalities. Furthermore, it is well known that physiologic influences, especially when excessive, may provoke electrocardiographic abnormalities, and that hormonal, chemical, and toxic stimuli, as well as certain deficiencies, may produce temporary but striking changes in the QRST complex. Indeed, the changes may be profound and irreversible, and incompatible with survival. More and more attention is being directed to the effect of abnormal electrolyte patterns, and the practical application of this aspect of electrocardiography is becoming increasingly important.

It is evident, then, that to define the normal electrocardiogram is a

*From the Electrocardiographic Laboratory, Beth Israel Hospital, and the Harvard Medical School, Boston, Massachusetts.

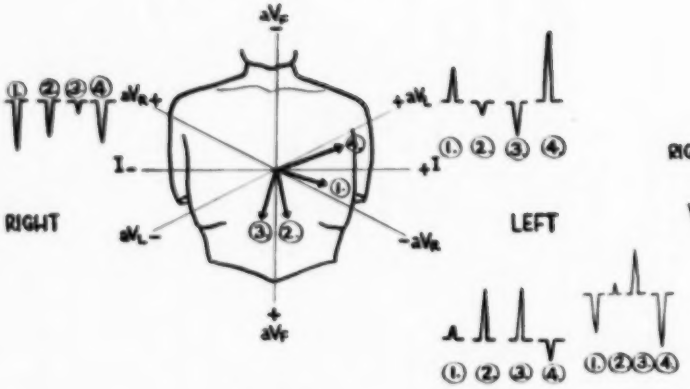

FIG. I

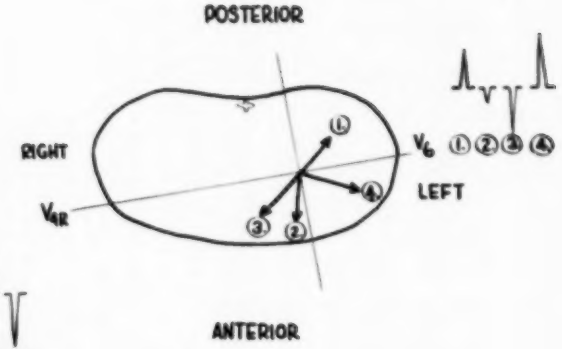

FIG.2

Figure 1: Frontal plane projections of four cardiac vectors (1, 2, 3, 4) on the limb leads I, aVR, aVL, and aVF. See text.

Figure 2: Horizontal plane projections of four cardiac vectors (1, 2, 3, 4) on the precordial leads V_4r and V_6. See text.

difficult task, and I will make no attempt to do so; ample descriptions of an empirical or more fundamental kind may be found in the numerous publications on the subject. Those who devote but little time to the study of electrocardiography seek a handy set of rules to guide them in interpretation. Unfortunately, very few rules can be formulated that are sufficiently universal to attain practical significance.

Although right and left axis deviation are accepted as normal, left axis deviation in infants, and right axis deviation in elderly people are probably abnormal. Upright T waves in lead I and the left sided precordial leads, and inverted T waves in lead aVR are so constant in the normal electrocardiogram, that any departure from this pattern must be viewed as an abnormality. Q waves may occur in any of the leads, except those on the right side of the precordium, and QS deflections in Ve and V_1 should be looked upon with suspicion. The ST segments are normally at the isoelectric level, or slightly elevated.

In spite of the detailed descriptions of the normal electrocardiogram, which are available, difficulty in distinguishing between normal and abnormal tracings is frequently encountered, the most common interpretive problems being the following:

(1) Vertical heart vs posterior myocardial infarction.
(2) "Normal" right axis deviation vs right ventricular hypertrophy.
(3) "Normal" incomplete right bundle branch block vs right ventricular hypertrophy.
(4) "Normal" left axis deviation vs left ventricular hypertrophy.
(5) Normal vs incomplete left bundle branch block.

Considerable help in electrocardiographic interpretation may be obtained by determining, so far as it is possible, the spatial position of the initial and final depolarization forces. For this purpose, leads which are parallel to the three natural coordinate axes of the body, X, Y, and Z, may be utilized.

The horizontal direction (X) of the cardiac vector can be obtained by inspecting lead I, or by comparing leads V_3r or V_4r with V_6. A q deflection in lead I, or initial r deflections in V_3r or V_4r combined with q waves in V_6 indicate rightward deviation of the initial depolarization vectors (Figures 1 and 2).

The vertical direction (Z) of the cardiac vector is revealed by the unipolar limb leads. An initial positive deflection in aVF and an initial negative deflection in aVR and/or aVL indicate that the earliest forces of depolarization point downward. The reverse direction is indicated if the first deflection of the QRS group in lead aVF is negative (Figure 1).

A bipolar sagittal lead may be employed to determine the sagittal direction (Y) of the initial depolarization forces. An electrode is placed below the costal margin in the right anterior axillary line and is connected to the B pole of the galvanometer; it is paired with a second electrode placed at the same body level in the right posterior axillary line and connected to the A pole of the galvanometer. Positivity of the first QRS deflection denotes an anterior, and negativity of the first QRS deflection, a posterior

direction of the initial depolarization forces (Figure 3).

The spatial position of the terminal depolarization forces can be determined in the same manner by utilizing the final deflections of the QRS group.

Our studies in vectorcardiography have impressed us[1] with the importance of the spatial position of the initial and final depolarization forces in solving the problems mentioned above, and we have attempted to apply the results of our observations to electrocardiographic interpretation. The following is a tentative and brief summary of some of our observations:

(1) Clockwise rotation of the heart around its longitudinal axis occurs when the heart is in a vertical position.

(2) Counter-clockwise rotation of the heart around its longitudinal axis occurs when the heart is in a horizontal position.

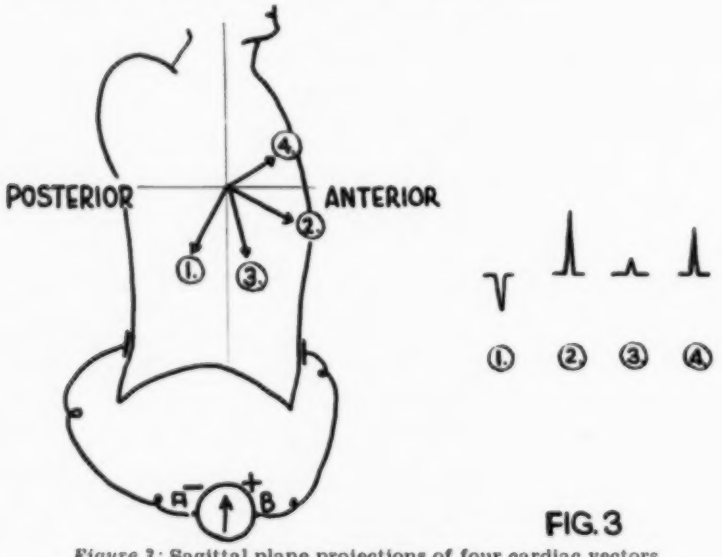

Figure 3: Sagittal plane projections of four cardiac vectors (1, 2, 3, 4) on a sagittal lead. See text.

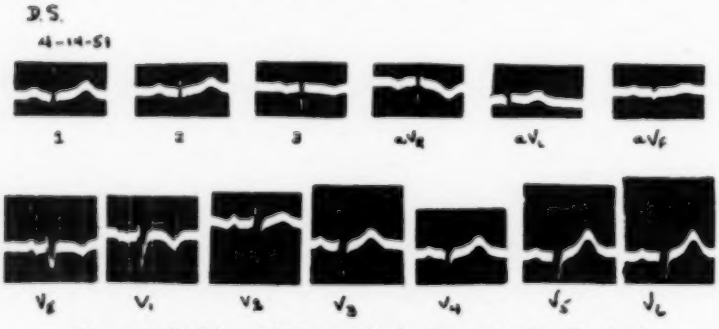

Figure 4: Right and left ventricular hypertrophy. See text.

(3) Excessive clockwise rotation suggests right ventricular hypertrophy, especially in the presence of right bundle branch block.
(4) Clockwise rotation in a horizontal heart is noteworthy, and suggests right ventricular hypertrophy.
(5) Excessive counter-clockwise rotation suggests left ventricular hypertrophy.
(6) Counter-clockwise rotation in a vertical heart is noteworthy and suggests left ventricular hypertrophy.
(7) The initial forces in a normal heart point somewhat to the right, anteriorly, and up or down.
(8) The initial forces in uncomplicated right bundle branch block, complete or incomplete, are similar to those for the normal heart.
(9) The initial forces in uncomplicated left bundle branch block, complete or incomplete point to the left, anteriorly, and down.
(10) The terminal forces in uncomplicated right bundle branch block are oriented to the right, superiorly, and anteriorly.
(11) The terminal forces in incomplete right bundle branch block complicated by left ventricular hypertrophy are oriented to the right, superiorly, and posteriorly. In many of these, right bundle branch block is simulated but actually is not present.

Right axis deviation usually is an indication that the heart position is vertical, left axis deviation usually means a horizontal position. Rotation of the heart around its longitudinal axis is recognized by the character of the initial QRS deflections, and the position of the transitional zone. Marked clockwise rotation is characterized by the absence of Q waves in

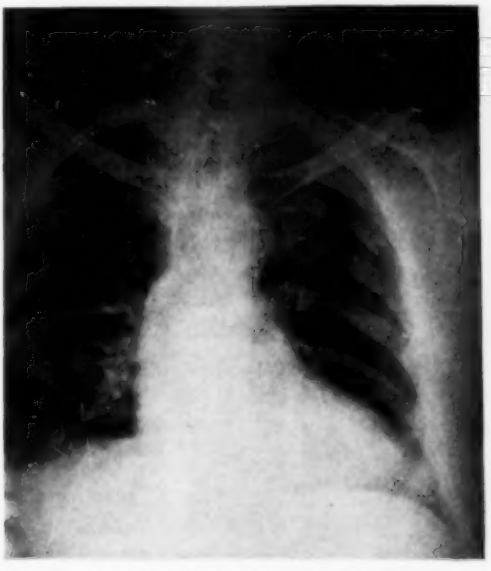

Figure 5: Seven foot heart film from same patient as Figure 4.

leads I and aVL, absent or tiny Q waves in V_5 and V_6, and initial negative or very tiny r deflections in aVR and V_1; the transitional zone is displaced to the left. Marked counter-clockwise rotation is distinguished by the presence of Q waves in leads I, aVL, and V_3 or V_4, as well as V_5 and V_6, and rather large initial r waves in the right sided precordial leads; the transitional zone is displaced to the right. When the electrocardiographic signs of position and rotation are equivocal, the method of analysis here described should not be attempted. The signs may be obscured by anterior or posterior displacement of the heart, localized myocardial disease, anomalous atrioventricular excitation, lack of remoteness from the heart of some electrode positions, and discordance.[1]

The electrocardiogram shown in Figure 4 illustrates some of these points. The tracing appears to be normal, and, therefore, the roentgenogram of the heart is rather surprising (Figure 5); subsequent autopsy examination revealed right and left ventricular hypertrophy. The contrast between the apparently normal electrocardiogram and the gross cardiac enlargement is striking. However, if the electrocardiogram is scrutinized from the point of view of the three dimensional direction of the initial and terminal forces, it can be interpreted as combined right and left ventricular hypertrophy; it simulates incomplete right bundle branch block. There is evidence of clockwise rotation of the heart around its longitudinal axis, a feature which is characteristic of right ventricular hypertrophy when the heart is in the horizontal position.[2] The diagnosis of left ventricular hypertrophy is indicated because the terminal forces are directed posteriorly, and not anteriorly as is true in ordinary right bundle branch block or isolated right ventricular hypertrophy. As a consequence of the posterior, rightward and superior position of the terminal forces the customary R′ deflection in V_1 is missing, and is represented by a small notch on the ascending limb of

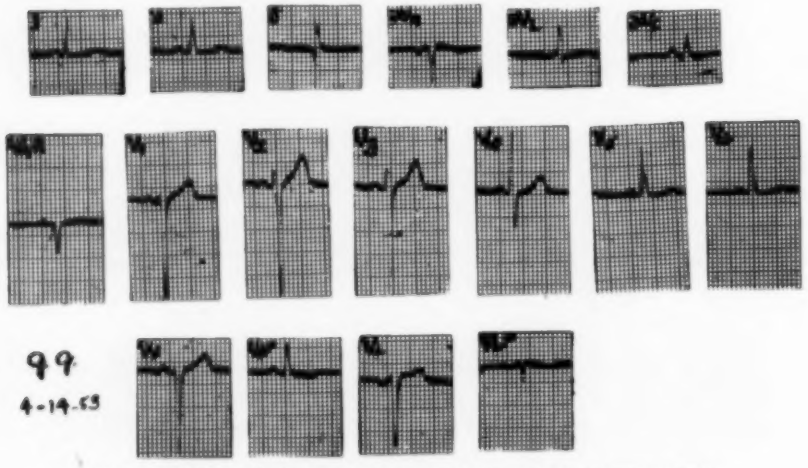

Figure 6: Normal electrocardiogram interpreted as incomplete left bundle branch block. See text.

the S wave; it emerges as a bona fide deflection when the electrode is moved to higher interspaces. This final positive deflection, therefore, is conspicuous in lead aVR. Another consequence of the unusual orientation of the terminal forces is the final small S wave in lead V_6.

The electrocardiogram shown in Figure 6 was interpreted as normal. However, when the criteria mentioned above were applied, the diagnosis was changed to incomplete left bundle branch block. A vectorcardiogram was then obtained, and was consistent with this conduction defect.[2] We believe that incomplete left bundle branch block is much more common than is realized, and is usually mistaken for a normal electrocardiogram, left ventricular hypertrophy, or anterior myocardial infarction.

SUMMARY

The present generally accepted definition of the normal electrocardiogram is inadequate. In many instances the spatial position of the initial and terminal depolarization forces can be determined from the electrocardiogram. This knowledge can be applied to a clearer differentation of normal electrocardiograms and certain abnormal states.

RESUMEN

La definición actualmente aceptada del electrocardiograma normal, es inadecuada. En algunos casos la posición especial de las fuerzas de polarización inicial y terminal, pueden ser determinadas por el electrocardiograma. Este conocimiento puede aplicarse para una más clara diferenciación del electrocardiograma normal y el de ciertos estados anormales.

RESUME

La définition de l'électrocardiogramme normal, telle qu'elle est généralement comprise actuellement, n'est pas exacte. Dans de nombreux cas, la position spatiale des forces dépolarisantes initiales et terminales peuvent être déterminées par l'électrocardiogramme. Cette notion trouve son application pour établir une différence plus nette entre les électrocardiogrammes normaux et certains états pathologiques.

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Some Aspects of Electrocardiography in Infants and Children with Congenital Heart Disease

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Certain types of laboratory procedures yield information so conclusive that there can be little if any question as to the clinical significance of the data obtained. Other types of laboratory data have inferential value and depend for their specificity upon descriptive analyses, i.e., a statistical differential between comparable groups of normal and abnormal measurements. The electrocardiogram may be used to illustrate both types of information. With reference to the generation and conduction of cardiac impulses, or in clinical terms the cardiac rate and rhythm, the information derived from the electrocardiogram may be considered quite conclusive, at least in most circumstances. In the detection of myocardial abnormalities such as cardiac enlargement, more particularly single chamber hypertrophy, we must, if we are to be critically honest, admit that the electrocardiogram is as yet of largely inferential value. This is not to say that the inferences gained may not be so great as to be practically conclusive. What it does mean is that, lacking absolutely definitive data, diagnostic reliance will necessarily rest, at times insecurely, on descriptive and therefore somewhat empirical information.

In the study of the electrocardiogram of infants and children, one of the most important determinations is that of the relative size of the right and left ventricles. For this determination, and particularly to differentiate normal and abnormal, a descriptive analysis may be made of a variety of electrocardiographic measurements. Historically the first such attempt to determine abnormal degrees of right and left ventricular hypertrophy was to describe the extremity lead patterns in such terms as "axis deviation".[1] While this may have seemed useful in some cases, important discrepancies were frequently observed (Figure 1), explained by the more recent concept that the form of the ventricular deflections in the extremity leads represents mixtures of potential variations and is consequently influenced by other factors than just ventricular size.[3] The next logical step was to investigate the potential value of leads which were considered to be less dependent on other factors than ventricular size. These of course were the precordial leads, particularly those of so-called unipolar derivation,[2] which are believed to record primarily the potential variations derived from the epicardial surface of that part of the heart immediately underlying the exploring electrode. Statistical analyses of various measurements from such leads have been made in normal infants and children[4] and are being studied in comparable groups of infants and children with various types of heart disease. While it is not within the intended scope of this

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paper to review the details of these studies, it should be of interest to note certain characteristic patterns and their diagnostic importance.

An important sequence of electrocardiographic changes in newborn infants is that which occurs during the first 24 to 48 hours in the unipolar precordial leads (Figure 2). This is the reversal of the T wave vector without comparable changes in the initial ventricular deflections. While the exact significance of these normal changes is still in question, the interesting fact is that the precordial lead pattern seen normally during the first 24 hours of postnatal life also constitutes a typical, though not previously recognized, pattern of pathological right ventricular hypertrophy particularly during infancy and early childhood. Examples of this and other patterns of right ventricular hypertrophy are shown in Figures 3 and 4.

The electrocardiographic detection of right ventricular hypertrophy has obvious diagnostic importance in such defects as pulmonary valvular stenosis and tetralogy of Fallot. It has prognostic importance in coarctation of the aorta, especially during early infancy.[7] In brief summary, right ventricular hypertrophy in an infant with uncomplicated coarctation of the aorta is believed to result from the dynamics of the fetal circulation when the ductus arteriosus inserts proximal to the region of coarctation. In this situation the strain placed on the right ventricle in-utero is relieved at birth with normal closure of the ductus arteriosus. Neonatal right-sided cardiac enlargement and failure are therefore retrogressive and do not require immediate surgical intervention (Figure 5). Furthermore, in these cases, adequate collateral circulation has presumably developed by the time of birth so that on assumption of the postnatal circulation the left ventricle does not dilate and fail. The prognosis in

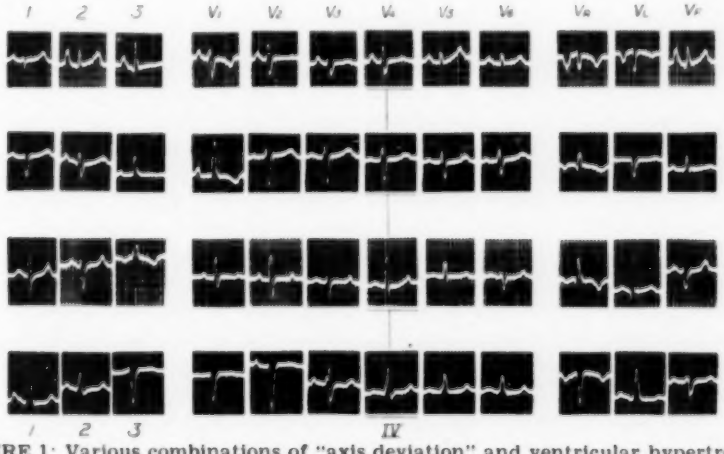

FIGURE 1: Various combinations of "axis deviation" and ventricular hypertrophy. From top to bottom, the first two electrocardiograms display right axis deviation with left and right ventricular hypertrophy respectively (tricuspid atresia and tetralogy of Fallot). The next two display left axis deviation with right and left ventricular hypertrophy respectively (common AV ostium with pulmonary stenosis and tricuspid atresia). Note also the similarity of a single precordial lead IV in the various situations and the obvious need for a full set of unipolar precordial leads.

this group is therefore good. Those babies, on the contrary, with otherwise uncomplicated coarctation of the aorta and left rather than right ventricular hypertrophy have a very poor prognosis, the majority dying during early infancy with progressive left ventricular enlargement and failure. In these infants it is believed that the fetal ductus inserted distal to the region of coarctation, thereby removing any stimulus to the development of a collateral circulation which would serve to protect the left ventricle after birth. Operation should therefore be done very early in these cases, probably using a temporary shunt from proximal to distal aorta during the procedure.

It has already been established[6] that particularly in infants electrocardiographic evidence of left ventricular hypertrophy is an important help in establishing the diagnosis of patent ductus arteriosus. The electrocardiogram is helpful, not by providing a pattern pathognomonic of the defect in question, but by demonstrating specific enlargement of the left ventricle when this (or even the detection of any cardiac enlargement) could not be determined by other technics such as x-ray examination.

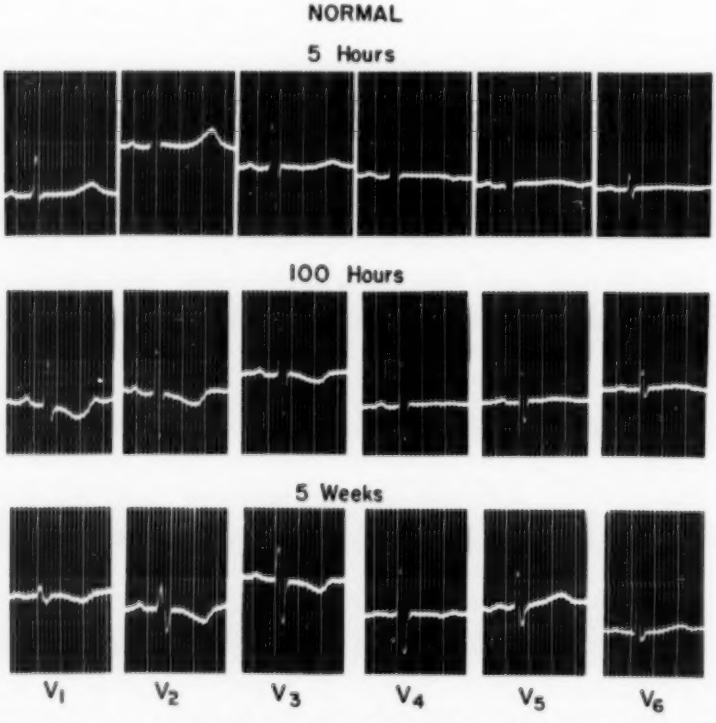

FIGURE 2: Normal precordial leads configuration at birth and the sequence of changes during early infancy. Note particularly the T wave pattern during the first day of life and its similarity to the pattern of right ventricular hypertrophy shown in Figure 3. (This illustration was previously published in Postgraduate Medicine, 13:141, 1943—Ziegler, R. F. et al: "The Diagnosis and Treatment of Congenital Cardiovascular Defects in Infants.)

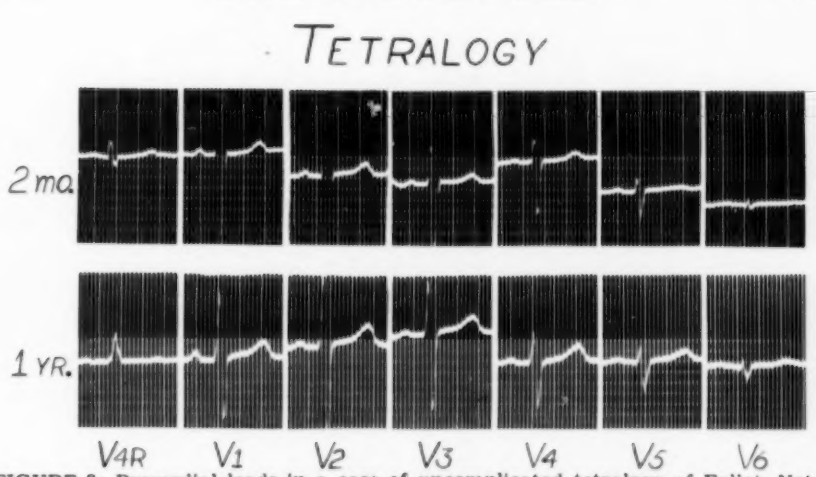

FIGURE 3: Precordial leads in a case of uncomplicated tetralogy of Fallot. Note the upright T waves in leads from the right side of the precordium and the flattened T waves in leads from the left side of the precordium. The QRS pattern, except for that in lead V_4R, is hardly diagnostic of right ventricular hypertrophy. This has proved to be a quite characteristic precordial lead pattern in babies with abnormal degree of right ventricular enlargement and later than the first day of postnatal life.

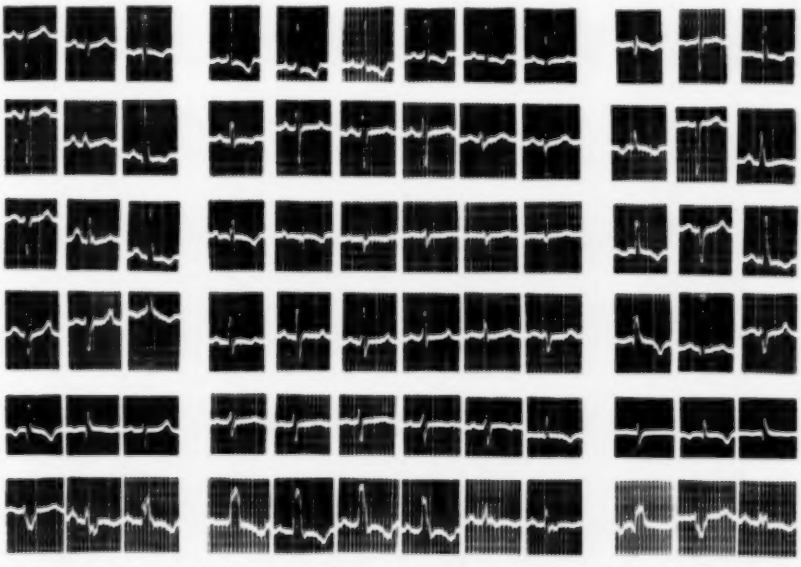

FIGURE 4: Various electrocardiographic patterns of right ventricular hypertrophy. The three leads on the left are standard extremity leads 1, 2, and 3; the three leads on the right are unipolar leads Vr, Vl, and Vf; the middle six leads are unipolar precordial leads V_1 through V_6. From top to bottom the clinical diagnosis of patients represented are: tetralogy of Fallot, tetralogy of Fallot, valvular pulmonary stenosis with closed interventricular septum and interauricular septal defect, common atrio-ventricular ostium with pulmonary stenosis, tetralogy of Fallot and complete situs inversus, valvular pulmonary stenosis with closed interauricular and interventricular septa.

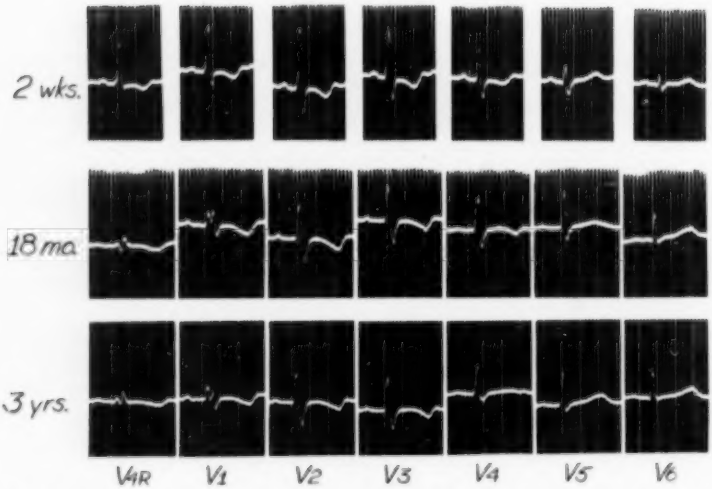

FIGURE 5: The precordial lead electrocardiogram in a child with uncomplicated coarctation of the aorta in whom the fetal ductus arteriosus inserted proximal to the region of coarctation and closed at birth. Note the initial pattern of right ventricular hypertrophy changing to that of right bundle branch block. The baby was in marked right-sided congestive heart failure at birth, regained cardiac compensation rapidly and completely with medical management, and was finally operated on successfully at the age of three and one-half years. (This set of electrocardiograms will also appear in the paper listed in Reference number 7.)

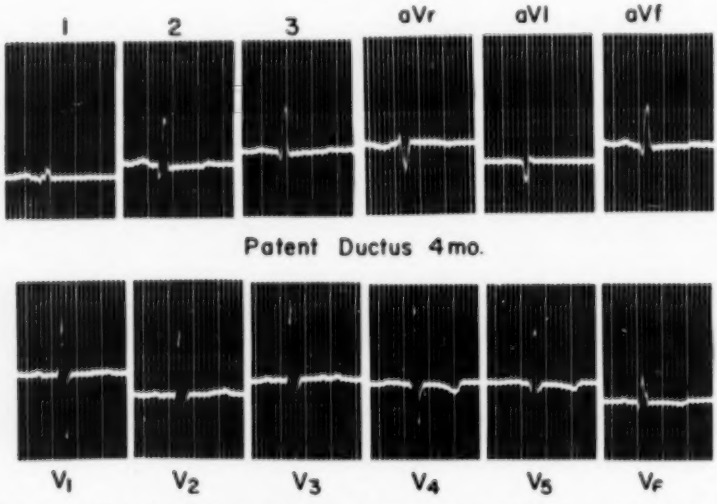

FIGURE 6: A typical electrocardiogram in an infant with uncomplicated patent ductus arteriosus. The precordial leads are characteristic of left ventricular hypertrophy. (This illustration was previously published in Postgraduate Medicine, 13: 141, 1953—Ziegler, R. F., et al: "The Diagnosis and Treatment of Congenital Cardiovascular Defects in Infants".)

Electrocardiographic evidence of right ventricular hypertrophy in suspected patency of the ductus arteriosus does not necessarily exclude this diagnosis but should alert the examiner to the need for a thorough cardiac evaluation including careful physiological studies before submitting the patient to operation.

It has been said that left ventricular hypertrophy in a child with cyanotic congenital heart disease is diagnostic of tricuspid atresia. While this may be true in many cases, it is by no means always so. Other cases have included transposition of the great vessels (with other combinations of defects), truncus arteriosus, complete valvular pulmonary atresia with closed interventricular septum, rudimentary right ventricle, and tetralogy of Fallot with combined right and left ventricular hypertrophy (not the so-called "pentalogy"). One electrocardiographic finding other than that of simple left ventricular hypertrophy has been observed sufficiently frequently in cases of tricuspid atresia to appear to have almost pathognomonic value when it occurs. This is a pattern which closely resembles that of the Wolff-Parkinson-White complex: short PR interval or segment, broadening of QRS, and absence of Q waves in leads from the left side of the precordium (Figure 7). The anatomy of the heart in tricuspid atresia might well account for this electrical pattern without invoking anomalous atrioventricular conduction as in cases with ventricles of more nearly equal size. Perhaps a more nearly accurate electrical characterization of the pattern described would be to relate it to a functional type of left bundle branch block.

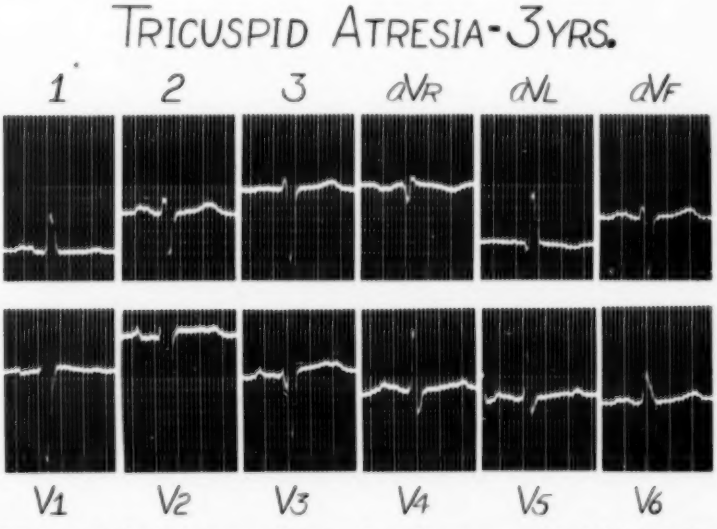

FIGURE 7: A typical electrocardiogram in a three year old child with tricuspid atresia. Note the similarity of the precordial lead pattern to that of left bundle branch block and the apparently short PR interval which resembles that of the Wolff-Parkinson-White complex.

SUMMARY AND CONCLUSIONS

1) Some of the characteristic electrocardiographic patterns in normal infants and in infants and children with operable forms of congenital heart disease are briefly reviewed.

2) One of the precordial lead patterns of right ventricular hypertrophy during early childhood is similar to that of normal infants during the first day of life. This is the pattern of upright T waves in leads from the right and flattened T waves in leads from the left side of the precordium.

3) The prognostic significance of right ventricular hypertrophy in infants with uncomplicated coarctation of the aorta is reviewed.

4) The diagnostic value of the electrocardiogram in patent ductus arteriosus is briefly summarized.

5) A characteristic precordial lead pattern is described in typical cases of tricuspid atresia. This consists of broad P waves, short PR interval or segment, broad QRS, absence of Q waves and late activation in leads from the left side of the precordium.

RESUMEN Y CONCLUSIONES

1) Se revisan brevemente algunas caracteristicas de los aspectos electrocardigráficos en los infantes normales y en los infantes y niños con formas operables de enfermedades del corazón congénitas.

2) Una de las precordiales de la hipertrofia ventricular durante la primera infancia, es similar a la de los niños normales durante el primer dia de la vida. Este es el patrón de ondas T elevadas en las tomadas del lado derecho y T aplanadas en tomas del lado izquierdo del precordial.

3) La significación pronóstica de la hipertrofia ventricular derecha en infantes con coartación no complicada de la aorta, se revisa.

4) Se resume el valor diagnóstico del electrocardiograma en ductus arteriosus permeable.

5) Se describe una precordial caracteristica de la atresia tricúspide. Esta, consiste en amplias ondas P, corto intervalo o segmento PR, ancha QRS, ausencia de onda Q y activación tardia en las tomas a la izquierda del área precordial.

RESUME

1) L'auteur passe rapidement en revue les caractères des tracés électrocardiographiques chez les nouveaux-nés normaux et chez les nouveaux-nés et les enfants atteints de cardiopathies congénitales opérables.

2) Une des dérivations précordiales donne, dans le cas d'hypertrophie ventriculaire droite au cours de la première enfance, un tracé semblable à celui du nouveau-né normal au moment de sa naissance. Il s'agit d'une surélévation de l'onde T dans les dérivations précordiales droites, et un applatissement de l'onde T dans les dérivations précordiales gauches.

3) L'auteur examine la signification pronostique de l'hypertrophie ventriculaire droite chez la nouveau-né lorsqu'elle est consécutive à un rétrécissement aortique non compliqué.

4) L'auteur résume rapidement la valeur diagnostique de l'électrocardiogramme dans les cas de persistance du trou de Botal.

5) L'auteur décrit un tracé précordial caractéristique dans les cas d'atrésie tricuspidienne. Il consiste en de larges ondes P; intervalle PR court, complexe QRS large, absence d'onde Q et retard dans la dérivation précordiale gauche.

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The Electrocardiogram in Disturbances of Cardiac Rate and Rhythm

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The arrhythmias which we are going to discuss were selected for a double purpose: (a) to point out certain mechanisms and (b) to demonstrate that the correct interpretation of an arrhythmia is essential for the proper management of the patient.

Figure 1 shows a regular irregularity consisting of the formation of groups of two ventricular complexes throughout the record. At the bedside this arrhythmia could easily be mistaken for bigeminal rhythm due to premature systoles, whereas the electrocardiogram demonstrates that the disturbance is not due to extrasystolic impulse formation but to A-V block in the form of persistent 3:2 block. The recognition of the mechanism of this form of "bigeminal rhythm" precludes the use of an anti-arrhythmic drug like quinidine or procaine amide for which there is no indication. Such a disturbance of A-V conduction in recent posterior wall infarction —probably more common than bigeminy due to premature systoles—tends to be a transient phenomenon and does not call for any medication. The second record, obtained a few days later, shows normal 1:1 A-V conduction and evidence of healing of the posterior wall infarction.

Figure 2 shows again the formation of groups of two ventricular complexes ("bigeminal rhythm") in a patient with auricular flutter while receiving digitalis. Again, at the bedside the presence of bigeminal rhythm in a digitalized patient might suggest ventricular premature systoles as an expression of digitalis toxicity. Yet, to discontinue digitalis would be a mistake, since the electrocardiogram reveals that the "coupling" is not due to premature systoles but is the result of a desirable disturbance of conduction in the A-V junction, due to the blocking effect of digitalis. As was

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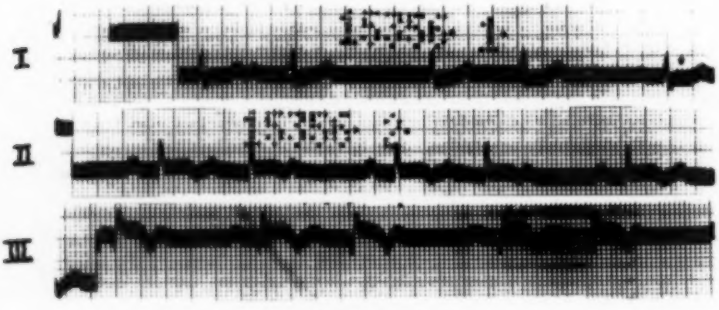

FIGURE 1

shown before[1] such "bigeminal rhythm" in auricular flutter can usually be accounted for by assuming a 2:1 A-V block high in the A-V junction and a 3:2 block with the Wenckebach phenomenon in the lower portion of the A-V junction affecting the alternate (conducted) impulses.

The following record (not illustrated) from an article by Miller et al.[2] demonstrates the effect of the intravenous administration of procaine amide on auricular flutter with 2:1 A-V conduction, and is shown as a warning against the use of procaine amide or quinidine in the initial treatment of auricular flutter. As the flutter rate of the auricles is slowed, 1:1 A-V conduction is established, giving rise to a very rapid

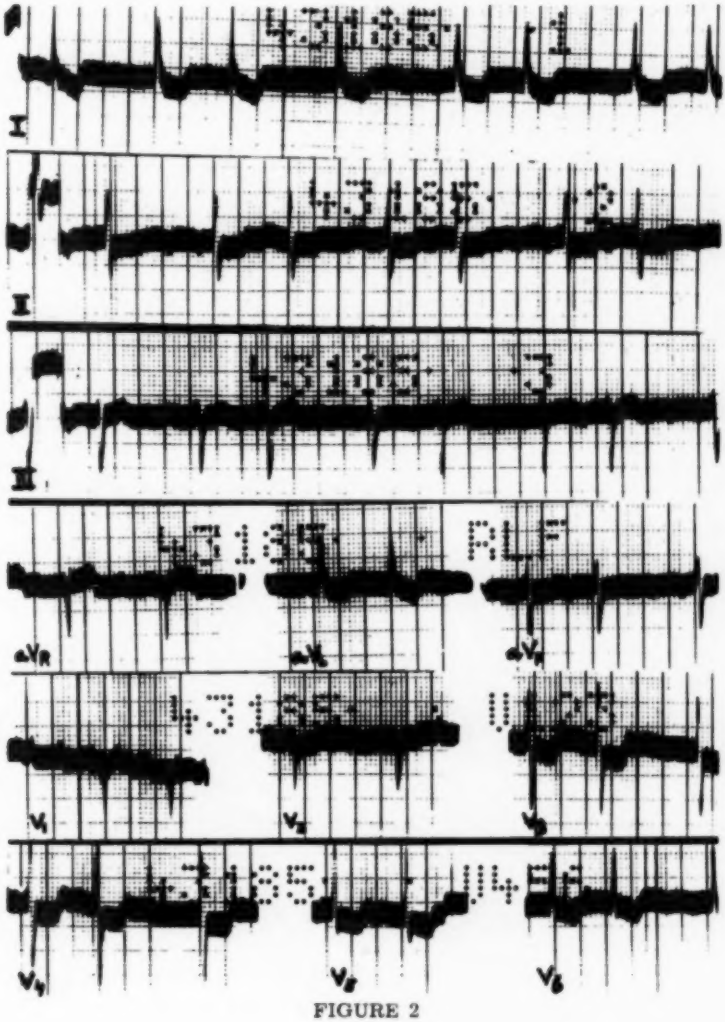

FIGURE 2

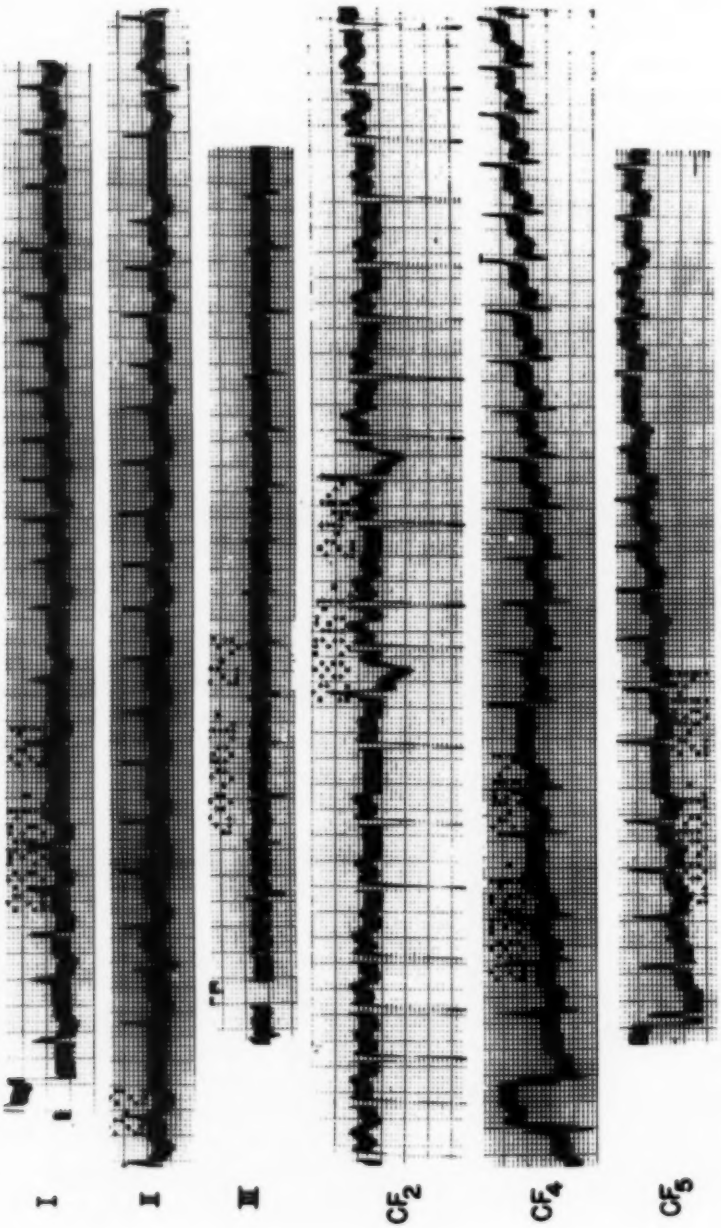

FIGURE 3

(From Langendorf, *American Heart Journal*, 1951)

ventricular rate. At the same time an intraventricular conduction disturbance develops, which gives the record the appearance of a ventricular paroxysmal tachycardia. The last strip shows the appearance of an A-V nodal rhythm after cessation of the auricular flutter. As a rule it is safer, and therefore preferable, to use digitalis in the initial treatment of auricular flutter.

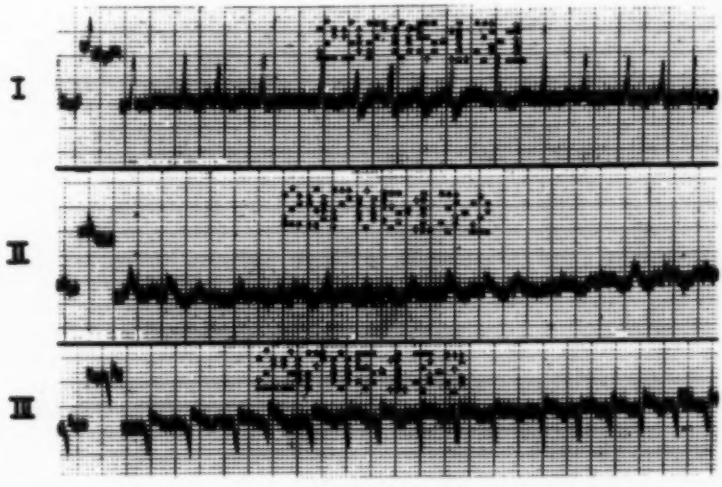

FIGURE 4

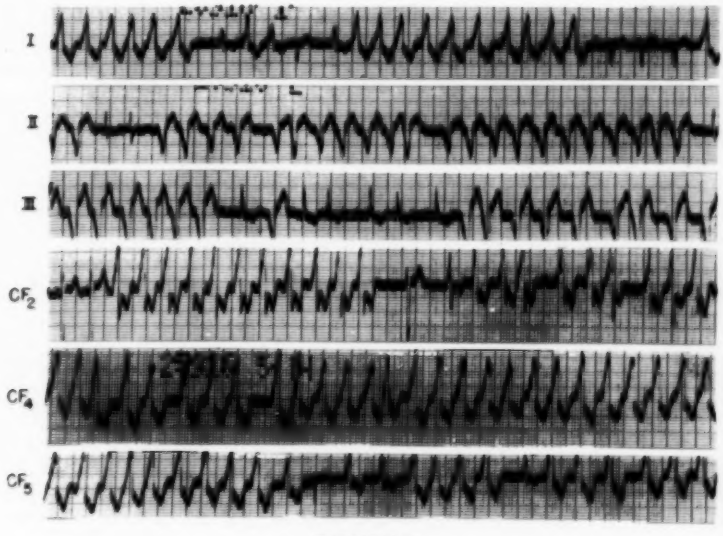

FIGURE 5

(Figures 4 and 5 from Langendorf, *Experimental Medicine and Surgery*, 1950)

Figure 3 demonstrates a common mechanism of aberrant conduction in auricular fibrillation with rapid ventricular rate. If a short ventricular cycle follows a long cycle the beat that terminates the short cycle tends to exhibit aberrant conduction as a result of lengthening of the refractory period following the long cycle. Such aberrant complexes should not be mistaken for ventricular premature systoles; they are characterized by a right bundle branch block pattern in the great majority of cases, by the absence of "fixed coupling" and by the absence of a longer pause following the bizzarre beat.[3] Occasionally this mechanism may initiate a whole run of similar aberrant complexes, imitating a ventricular paroxysmal tachycardia;[4] this is shown in Figure 4. Such an aberration is no contraindication for the use of digitalis; on the contrary, as the average ventricular rate slows, the bizzarre complexes disappear.

Figure 5 shows again an instance of auricular fibrillation with rapid ventricular rate and bizzarre ventricular complexes occurring in runs, suggesting ventricular paroxysmal tachycardia. Here, the slurring of the first portion of QRS, the frequent occurrence of transitional complexes (fusion beats), the absence of a longer pause after a run of bizzarre beats and the failure of digitalis to slow the ventricular rate should make one suspect the combination of auricular fibrillation and Wolff-Parkinson-White syndrome.[5] Comparison with a previous record taken during sinus rhythm, reveals the identical contour of the bizzarre beats recorded during auricular fibrillation with the beats exhibiting short P-R interval and prolonged QRS complex during sinus rhythm; thus, the bizzarre beats during auricular fibrillation are identified as due to anomalous A-V conduction of auricular impulses and do not represent ventricular premature systoles. The best treatment in such cases seems to consist of simultaneous administration of digitalis and quinidine.

SUMMARY

We present (1) two examples of "bigeminal rhythm" not due to extrasystolic impulse formation but due to a disturbance in A-V conduction; (2) two instances of auricular fibrillation with runs of bizzarre beats imitating ventricular paroxysmal tachycardia, one due to aberrant ventricular conduction, the other due to anomalous A-V conduction in a case of Wolff-Parkinson-White syndrome; and finally, (3) one case of auricular flutter with 2:1 A-V conduction who developed transient 1:1 A-V conduction with a rapid ventricular rate after procaine amide medication. The therapeutic implications of the correct diagnosis of the cardiac arrhythmias are pointed out.

RESUMEN

Presentamos (1) dos ejemplos de ritmo "bigeminado" no debido a formación de impulso extrasistólico, sino a trastornos de la conducción en A-V; (2) dos casos de fibrilación auricular con series de latidos bizarros que imitan la taquicardia ventricular paroxística, uno debido a conducción ventricular aberrante, el otro debido a conducción anómala A-V en un caso

de síndrome de Wolff-Parkinson-White y finalmente, (3) un caso de "flutter" con conducción 2:1 A-V que desarrolló conducción transitoria 1:1 A-V con rápida frecuencia ventricular después de medicación con la procainamida. Sé señala la importancia del diagnostico exacto de las arritmias para su terapeutica correcta.

RESUME

L'auteur rapporte deux observations de rythme bigéminé dont l'origine n'est pas une extrasystole, mais un trouble de la conduction auriculo-ventriculaire.

Il présente deux cas de fibrillation auriculaire avec des séries de battements curieux simulant la tachycardie ventriculaire paroxystique. Dans l'un il s'agissait d'une conduction ventriculaire aberrante, dans l'autre d'une anomalie de la conduction auriculo-ventriculaire d'un syndrome de Wolff-Parkinson-White.

Enfin, l'autre consiste en un cas de flutter auriculaire au rythme 2-1, qui se transforma en rythme 1-1 transitoire avec accélération ventriculaire à la suite d'un traitement par l'amide procaïnique. L'auteur insiste sur les conséquences thérapeutiques qu'entraine un diagnostic d'arythmie cardiaque correctement établi.

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Diagnostic Electrocardiographic Patterns*

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The term "diagnostic," as applied to electrocardiographic patterns, is not too well defined, and can be the subject of much controversy. However, as used here, "diagnostic" includes all types of electrocardiograms, which are of distinct help in the establishment of a clinical diagnosis.

Figures 1 and 2 are merely illustrative of tachycardias and arrhythmias. One hundred different arrhythmias could be demonstrated, but two will serve as examples. The first (Figure 1) is *ventricular tachycardia*. The wide, notched, slurred, bizarre character of the QRS is seen. Often, P (auricular) waves appear; they occur regularly, but at a rate entirely different from that of the ventricles. The auricular rate is slow, the rate of the ordinary regular sinus rhythm, whereas the ventricular rate is rapid, usually 160 beats or more per minute. The diagnosis of ventricular tachycardia is best made by means of the electrocardiogram. The second (Figure 2) is a *partial heart block*, with dropped beats,—actually a two to one heart block. The diagnosis of heart block, too, can practically be made only by the electrocardiogram. Indeed, the diagnosis of all the arrhythmias is chiefly, and sometimes, exclusively, dependent upon the electrocardiographic findings.

The electrocardiogram can be of help in the diagnosis of *valvular heart disease*. Figure 3 is the tracing of a patient with proved, long-standing chronic rheumatic cardiovalvular disease, and with mitral and aortic valve involvement. The abnormal P (auricular) waves and the tall R waves in lead aVF are an indication of right-sided enlargement, and, thus, suggestive of mitral valve disease. Characteristic of aortic valve disease is a high voltage of the QRS group. The electrocardiographic waves, then, often are suggestive or characteristic of disease of particular valves of the heart.

Recently, especially great interest in the diagnosis of *mitral stenosis* has developed, because valve commisurotomy is so frequently performed in appropriate cases. The electrocardiogram in Figure 4 is that of a patient whose murmur was characteristic of mitral stenosis. When the electrocardiogram disclosed a strain entirely of the right heart, the diagnosis was confirmed. The right axis deviation, with deep S-I, tall R-III, relatively tall R in lead aVF, and a right-sided pattern in the precordial leads, are all fairly good evidence of involvement chiefly of the right side of the heart. Hence, the clear inference can be drawn that mitral insufficiency or aortic insufficiency, if present, is of minor degree. Sole dependence, however, should never be placed on the electrocardiogram. Rather is it an aid, and occasionally a very great aid, to clinical diagnosis.

Pericarditis produces a characteristic electrocardiogram. This is illustrated in Figure 5. In leads I, II, III and in the precordial leads V_2-V_6, there appear RS-T elevations, which progressed to inverted T-waves; the RS-T

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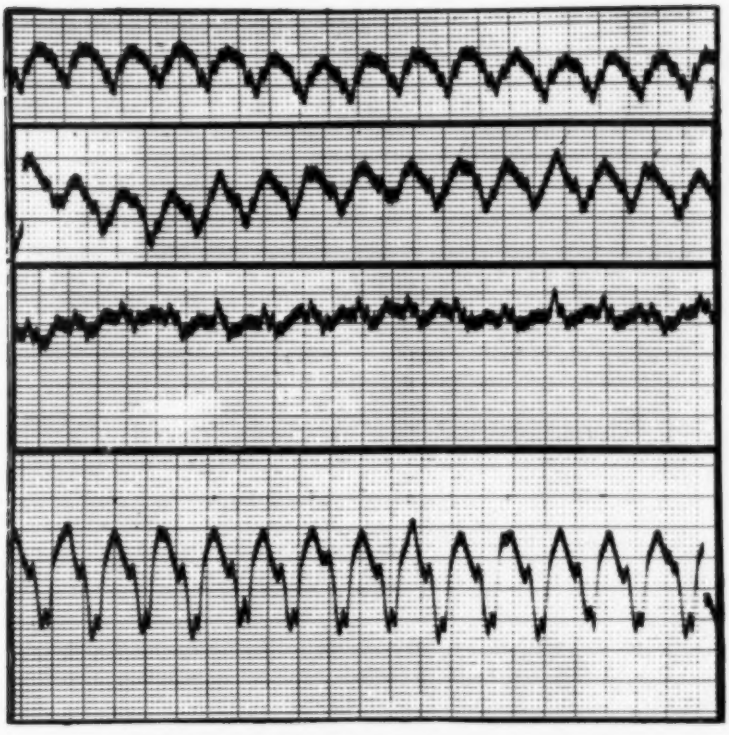

FIGURE 1: Paroxysmal ventricular tachycardia.

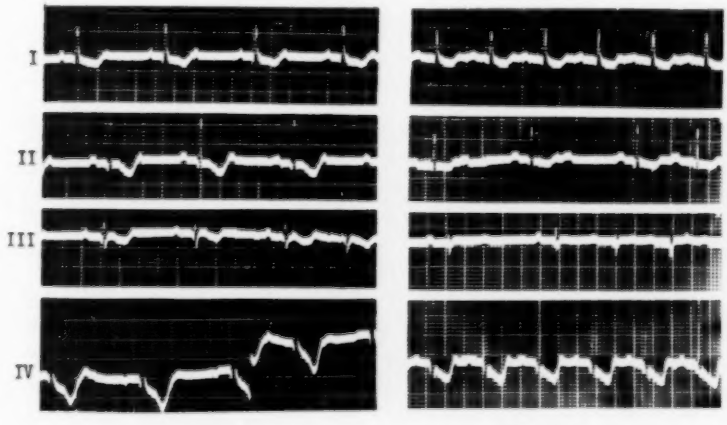

FIGURE 2A FIGURE 2B

Figure 2: G.M., w, 59. Digotoxin intoxication.
(A) December 15, 1945, 2:1 heart block. RS-T depressions and T-wave inversions all leads.—(B) December 18, 1946, sinus tachycardia alternating with 2:1 heart block. RS-T depressions and T-wave inversions not quite as pronounced.

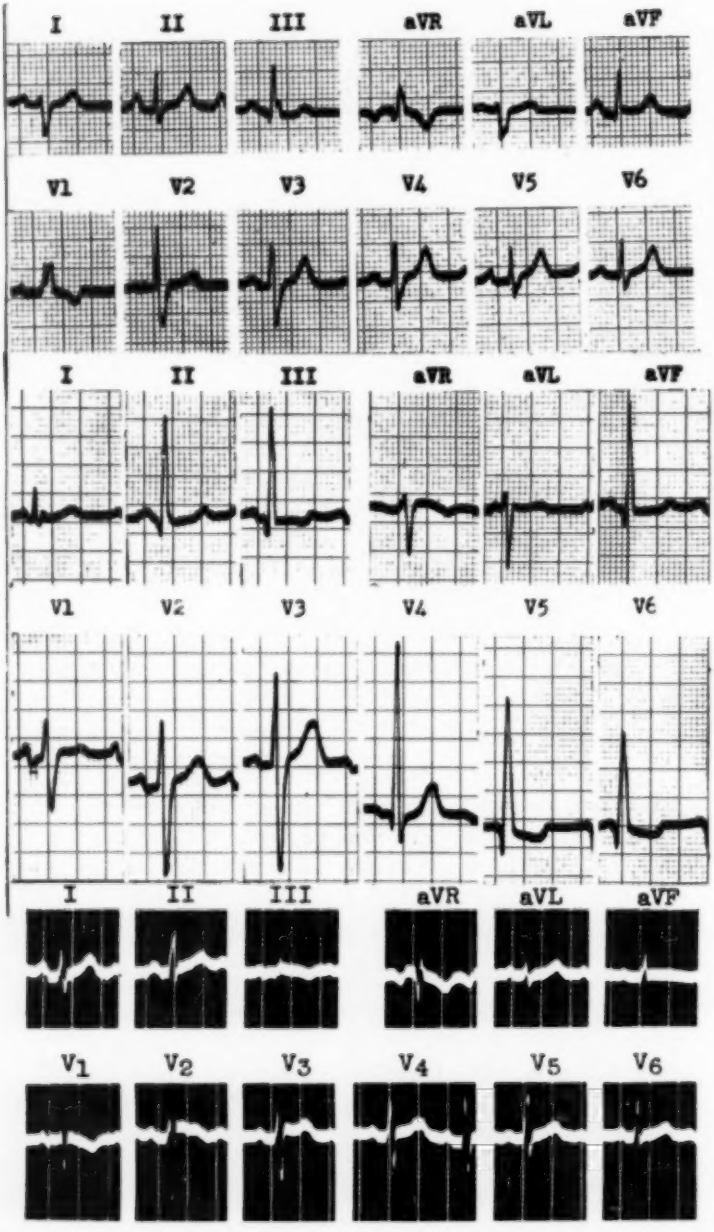

FIGURE 3 *(Center)*: M.R., f, 30. CRCVD, M and A valve involvement.—FIGURE 4 *(Upper)*: V.R., f, 32. CRCVD with M valve involvement.—FIGURE 5 *(Lower)*: D.W., m, 42. Acute non-specific pericarditis. Record taken on fifth day shows slight RS-T elevation in the standard leads, aVF, and V_2-V_5.

elevations are concordant in all these leads. Furthermore, no deep Q-waves are present. The concordant nature of the RS-T elevations, i.e., elevations but no depressions, and the absence of significant Q-waves are characteristic of pericarditis, and distinguish it from coronary occlusion.

Atypical *body habitus* often produces distinctive electrocardiograms. They are not diagnostic, but are often helpful. Thus, a long thin man usually possesses a long narrow chest, with a long narrow heart. The latter will produce a small QRS complex in Lead I, with a tendency to a right axis deviation. The frontal vector of the heart is almost at a right angle to Lead I; hence, the small QRS-I (Figure 6). Conversely, in an obese person with a high diaphragm, the transversely placed heart will produce a left axis deviation in the standard leads, with an inverted P wave and an inverted T wave in Lead III (Figure 7). This does not imply that this type of electrocardiogram will be found in every obese man or woman, or in every person with an elevated diaphragm and a transversely placed heart. If such an electrocardiographic tracing is disclosed, however, a diagnosis of a transversely placed heart may be made with some degree of certainty.

The 12-lead electrocardiogram shown in Figure 8 is representative of a big left ventricle, such as is found, e.g., in hypertension or in aortic insuf-

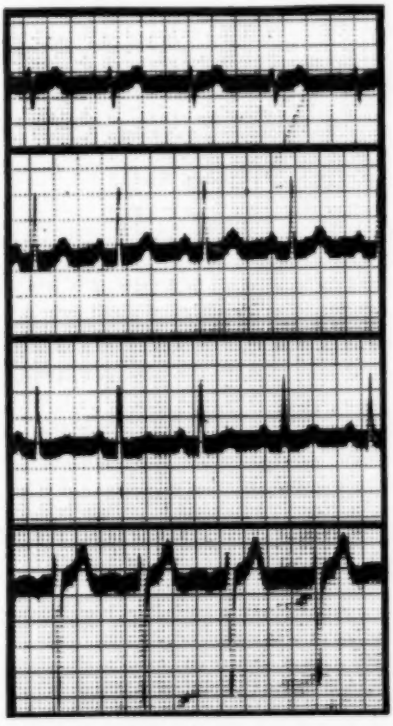

FIGURE 6: B.K., m, 34. Long narrow heart
(Lead I, II, III, IV, from above downwards)

ficiency. A high voltage of the QRS group can be seen, with RS-T depression and T wave inversion in Lead I; there is a delay in the appearance of the "intrinsic" deflection of the QRS group on the left side of the chest, in relation to the beginning of the QRS deflection. This, usually, is manifest in the left precordial leads, V_4, or V_5, or V_6, or V_7. The delay in the "intrinsic" deflection is explained by the thickness of the left ventricular muscle. In the right precordial leads, i.e., V_1 or V_2, no delay occurs.

The electrocardiogram of *bundle branch block* is specific. Figure 9 is an electrocardiogram characteristic of a *left bundle branch block*. The diagnosis of this condition is based almost solely on the electrocardiographic findings. A left axis deviation occurs, with a wide, notched, slurred QRS. The QRS complex and the T wave have a diphasic character. Thus, when the main deflection of the QRS is up or positive, the T wave is inverted or negative, and vice versa. Furthermore, there is a distinct delay in the appearance of the "intrinsic" QRS deflection on the left side of the chest, i.e., precordial leads in V_4 or V_5 or V_6 or V_7, in relation to the beginning of the QRS deflection, as compared with the right-sided precordial leads. Because of the *left* bundle branch block the delay is on the left side; in a right bundle branch block, this delay appears on the right side.

In "acute cor pulmonale" (Figure 10), a typical pattern has been described: a deep S-I, a deep Q-III, and an inverted T-III. When this condition does appear, it is highly suggestive of an acute right heart strain, which occurs, e.g., in pulmonary infarction or embolism. However, in almost two-thirds of the cases of pulmonary infarction or embolization, the electrocardiographic changes associated with coronary insufficiency are found. The "strain" is not, as many believe, on the right heart, but rather on the left ventricle. Hence, the appearance of RS-T depression and/or T wave inversion does not exclude acute cor pulmonale, but may rather be confirmatory of that clinical diagnosis.

Figure 11 is an electrocardiogram of a patient with long-standing bronchial asthma. It is indicative of *chronic right-sided enlargement of the heart*. The deep S-I and tall R-III, i.e., right axis deviation of the QRS group in the standard limb leads, and also the relatively tall R in lead aVF in the unipolar extremity leads, are all signs of right-sided enlargement in the frontal plane. The chest or precordial leads, which register the heart beat in the horizontal plane, also disclose relatively tall R waves on the right side, i.e., in V_1 and V_2, and relatively large S waves on the left side, i.e., in V_4, V_5, or V_6.

When there is an increase in the size of the right heart, abnormal P (auricular) waves are often observed, particularly in Leads II and III. In valvular heart disease, the P waves are wide and notched, often diphasic, and not infrequently tall. In pulmonary disease, the P waves are usually tall and pointed, rather than wide and notched.

Figure 12 is the electrocardiogram of a patient who suffered from the Tetralogy of Fallot, with associated enlargement of the right side of the heart. The x-ray of the heart was very suggestive of the condition, having a "wooden shoe" ("coeur en sabot") appearance. In the electrocardiogram,

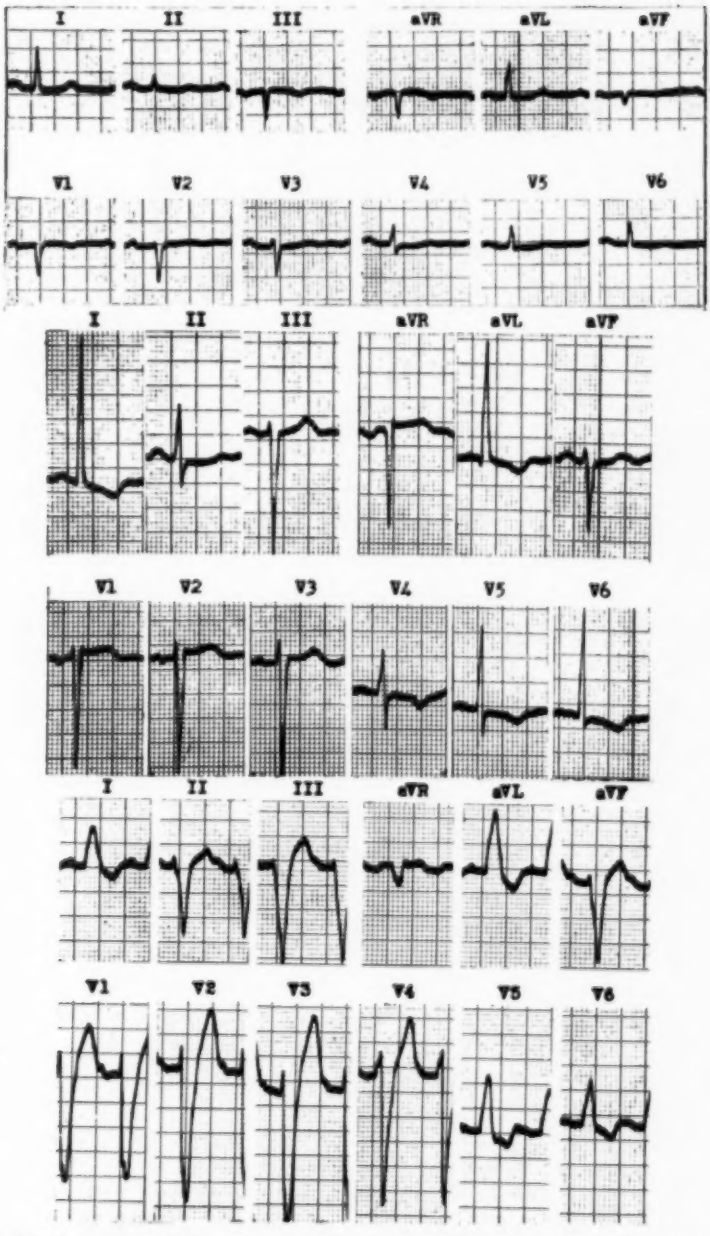

FIGURE 7 *(Upper):* M.G., f, 51. Obesity. — FIGURE 8 *(Center):* F.M., f, 65. Hypertension; enlarged heart, left vent. enlargement, vent. aneurysm. — FIGURE 9 *(Lower):* S.B., m, 60. Enlarged heart.

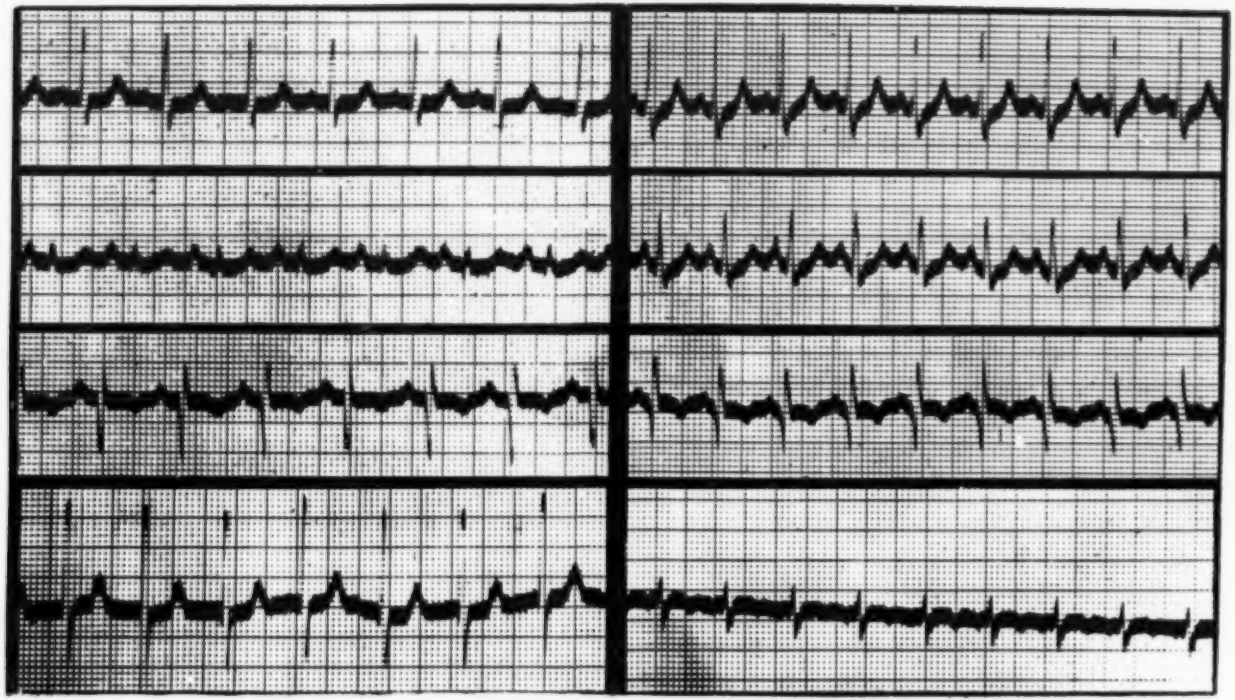

FIGURE 10A FIGURE 10B

FIGURE 10: (A) R.S., f, 70. Pulmonary artery embolism involving both main branches. Death after 18 hours. Electrocardiogram reveals left axis deviation with S-1 and a large Q-3; R-2 is low and notched, RS-T slightly depressed in all leads and T-3 inverted.—(B) B.M., f, 27. Pulmonary artery embolism involving both main branches. Death after eight hours. Electrocardiogram shows a deep S-1 and smaller S-2, large Q-3, depression of RS-T in the standard leads and inversion of T-3 and T-4.

all the evidences of right-sided enlargement are present: the deep S in Lead I, the tall R in Lead III, the relatively tall R in lead aVF, the relatively conspicuous R in the precordial leads V_1 and V_2, and the deep S waves in leads V_4 and V_5.

The tracing in Figure 13 could, indeed, confuse the electrocardiographer. It is an instance of "*Dextrocardia*".. All the waves in Lead I are reversed in direction, i.e., what is ordinarily upright or positive, is here downward or negative, and what is ordinarily downward or negative, is here upright or positive. Thus, the P wave, the main deflection of the QRS complex, and

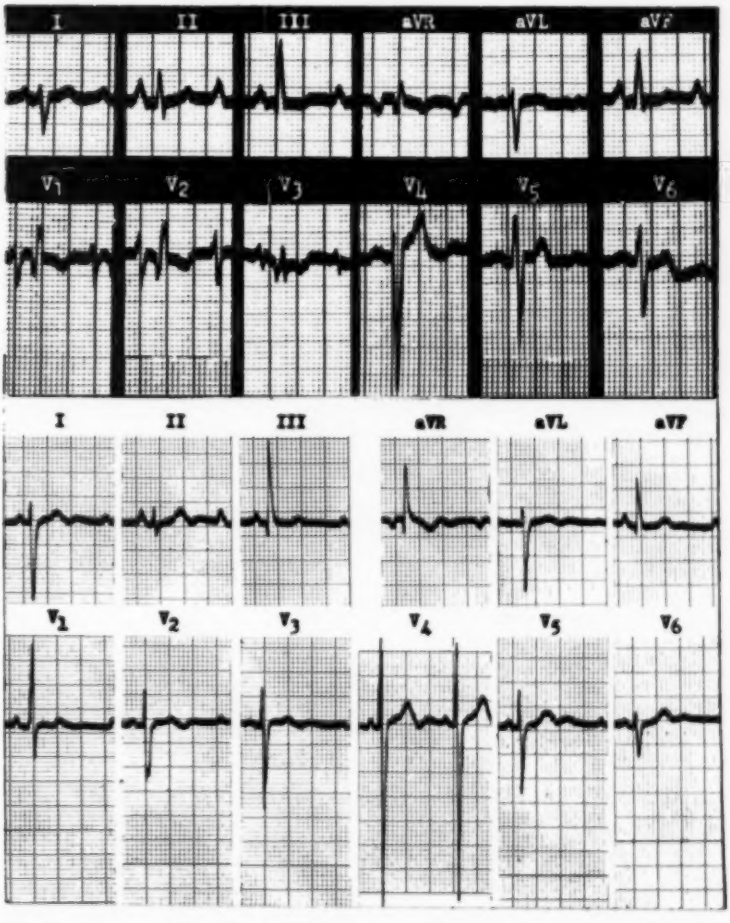

FIGURE 11 *(Upper)*: F.D., m, 52. Chronic cor pulmonale. Ecg shows high P-waves and evidence of right ventricular enlargement.—FIGURE 12 *(Lower)*: R.T., f, 8¼. Tetralogy of Fallot: murmur since birth, cyanosis, clubbing of finger tips, and dyspnea on exertion. Chest roentgenogram: coeur en sabot; peripheral lung markings decreased. Electrocardiogram reveals marked right axis deviation; tall R in V_1 and rS in V_6—evidence of right ventricular hypertrophy.

the T wave are all inverted in Lead I. In the lower row of Figure 13 a "normal" electrocardiogram is obtained by interchanging the electrodes for Leads I and II. A pattern of "Dextrocardia" can be obtained, whenever the nurse or technician mistakenly reverses Leads I and II, in recording the electrocardiogram of any patient. Before making an electrocardiographic diagnosis of "Dextrocardia," therefore, one should be certain that the right and left arm electrodes have not been interchanged.

In a patient suffering from congenital heart disease with *tricuspid atresia*, the right ventricle is small or atresic and, therefore, the *left* ventricle is

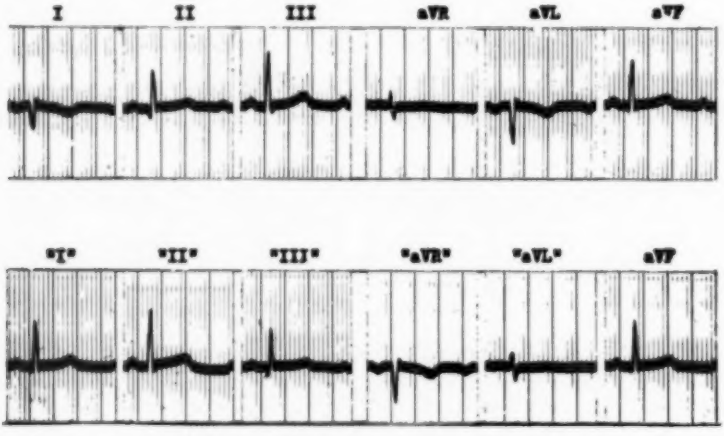

FIGURE 13: J.S., f, 14. Congenital dextrocardia; complete situs inversus.

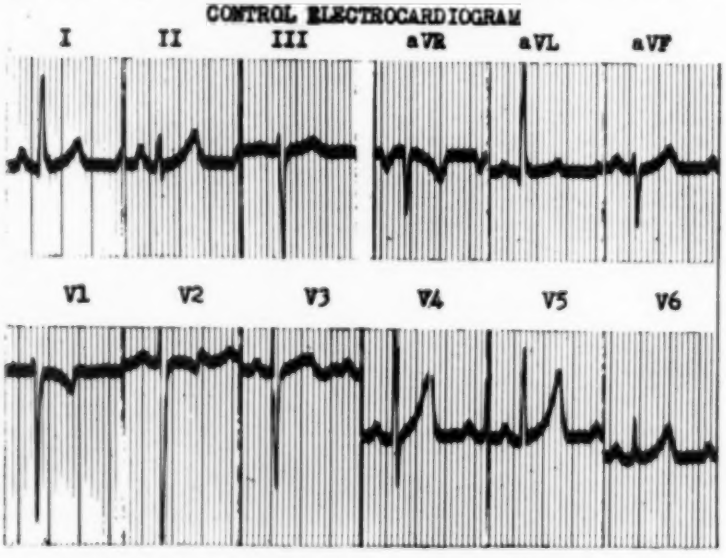

FIGURE 14: R.D., m, 5. Tricuspid atresia with left axis deviation.

greatly preponderant. In normal infants and in young children, the *right* ventricle is relatively preponderant. Hence, the occurrence of a left axis deviation, in a five year-old child, e.g., with obvious cyanosis, should immediately suggest the presence of a tricuspid atresia (Figure 14).

The electrocardiogram of "coronary insufficiency" is more or less characteristic. RS-T depressions and T wave inversions occur. RS-T elevations or deep Q waves (Figure 15) are not seen, except in aVR. In Figure 2 the electrocardiographic tracing of coronary insufficiency is one of digitalis intoxication, i.e., the RS-T depressions and the T wave inversions.

Coronary Occlusion

In coronary artery occlusion, an almost diagnostic electrocardiographic pattern is found. Thus, in Figure 16, there are deep Q waves and RS-T

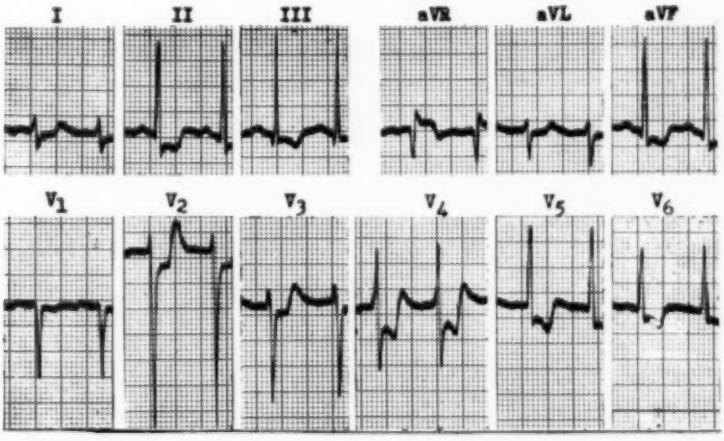

FIGURE 15: S.I., m, 42. Anginal syndrome due to coronary artery disease. Electrocardiogram taken during bout of chest pain. Dramatic RS-T depressions.

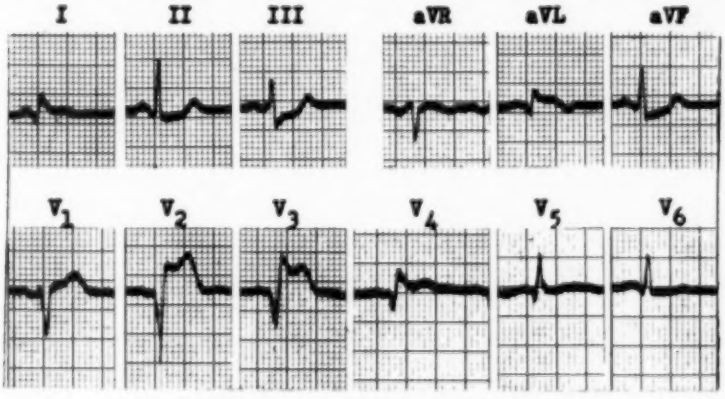

FIGURE 16: H.G. Acute coronary occlusion, second day. Anteroseptal infarction with characteristic changes in I, aVL, V_2-V_4.

elevations in Leads I, aVL, V_2, V_3, and V_4. This tracing is practically always indicative of anterior wall infarction, due to coronary artery occlusion.

In Figure 17, the electrocardiographic pattern is somewhat similar, but the deep Q waves and the RS-T elevations are present in Leads II, III, and aVF, rather than in Lead I, aVL, and the precordial leads. This is evidence of occlusive involvement of the diaphragmatic surface of the heart.

Ventricular Aneurysm

Significant Q waves and RS-T elevations, which remain unchanged, month in and month out, year in and year out, suggest the diagnosis of ventricular aneurysm. In this instance (Figure 18), the aneurysm is due to an old anterior wall infarction.

SUMMARY

The term "diagnostic" includes all types of electrocardiograms which are a distinct help in the establishment of a clinical diagnosis. The diagnosis of the various arrhythmias is chiefly and, sometimes exclusively, dependent upon the electrocardiographic findings. The electrocardiogram is of help

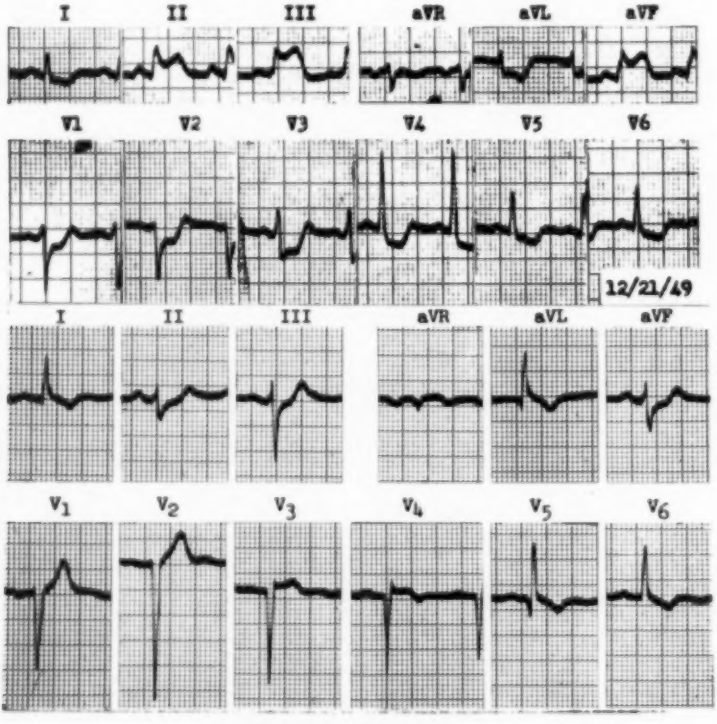

FIGURE 17 (*Upper*).

FIGURE 18 (*Lower*): H.L., m, 62. Coronary occlusion (February 1, 1948), with ventricular aneurysm. ECG still revealed RS-T elevations on December 24, 1952.

in valvular heart disease, particularly, mitral and aortic valve involvement. Pericarditis produces a characteristic tracing. A large left ventricle and large right ventricle produce characteristic electrocardiograms. Bundle branch block is an electrocardiographic diagnosis. The electrocardiogram is invaluable at times for the diagnosis of the congenital heart lesion; for example, to directly or indirectly confirm right side enlargement, destrocardia, tricuspid atresia, and so on. The electrocardiogram of coronary occlusion is almost pathognomonic.

RESUMEN

El término "diagnósticos" incluye todos los tipos de electrocardiogramas que son una definida ayuda para establecer el diagnóstico clínico. El diagnóstico de las diversas arritmias es principalmente y algunas veces exclusivamente dependiente de los hallazgos electrocardiográficos.

El electrocardiograma es útil en las afecciones valvulares del corazón, especialmente cuando están comprometidas las válvulas mitral y aórtica. La pericarditis produce un trazo característico.

También hay trazos característicos de crecimiento de ventrículos izquierdo y derecho. El bloqueo de ramas es un diagnóstico que depende del electrocardiograma. Este es a veces valiosísimo para el diagnóstico de las afecciones congénitas del corazón. Por ejemplo, para confirmar directa o indirectamente el crecimiento derecho, dextrocardia, atresia tricuspídea, etc.

El electrocardiograma de la oclusión coronaria es casi patognomónico.

RESUME

La valeur diagnostique d'un électrocardiogramme consiste en sa possibilité d'apporter un élément de secours pour établir le diagnostic clinique. C'est ainsi que le diagnostic de diverses arythmies dépend principalment et parfois même exclusivement des constatations électrocardiographiques. Le tracé rend service dans les affections valvulaires, particulièrement dans les altérations mitrales ou aortiques. La péricardite provoque un tracé caractéristique. Une augmentation de volume du ventricule gauche ou du ventricule droit est à l'origine d'un électrocardiogramme particulier. Le bloc de branche se diagnostique électrocardiographiquement. L'électrocardiogramme ne permet pas dans tous les cas d'aider au diagnostic de lésions cardiaques congénitales; par exemple, pour confirmer directement ou indirectement l'existence d'une augmentation des cavités droites, une dextrocardie, une atrésie tricuspidienne, etc. La courbe électrocardiographique de l'occlusi on coronarienne est à peu près pathognomonique.

Non-Diagnostic Electrocardiographic Patterns

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The title of this paper implies that certain aberrations may occur in electrocardiographic tracings which defy a diagnosis label. While these changes do not appear to fit a well-known pattern, it is well to remember that medicine is not practiced by electrocardiographic interpretations alone. The history, physical examination and other laboratory studies frequently aid in a sharper differentiation of electrocardiographic variations from the normal. Occasionally, serial studies alone may supply the necessary clues. We will present and clarify several so-called "non-diagnostic electrocardiographic patterns". In the main, all these changes are reversible with appropriate therapy.

Neurocirculatory Asthenia

This syndrome is of great significance to the cardiologist because more than half of the patients who consult him are suffering from an unnecessary anxiety about their hearts.

Symptoms are multiple and unrelated, and the more symptoms complained of, the less becomes the significance of each. In contra-distinction to the great number of symptoms, the signs are usually limited to tachycardia, tachypnea, unstable blood pressure, overactive heart action and a quick but sometimes roughened first apical sound. Occasionally, a transient zero level of diastolic pressure is obtained in the brachial arteries though it is normal in the lower extremities. It may be easily confused with aortic insufficiency. Cold moist extremities, axillary sweating, coarse tremors, absent gag and ocular reflexes, and hyperflexia also occur.

The electrocardiogram is perhaps most important because certain changes may appear which are commonly confused with organic heart disorders. The fact that electrocardiographic changes simulating myocardial infarction may occur in patients with neurocirculatory asthenia or hyperventilation syndrome is of paramount importance since most of them also have chest pain. Recent studies have expelled any uncertainty concerning the normality of the electrocardiogram in neurocirculatory asthenia. Variations are due to the presence of vertical heart position and the effects of exercise, body position and hyperventilation. Inversion of the T wave in Lead II and even in Lead III may be noted. The position of the heart is the most important causative factor of this finding since it occurs in the sitting or standing position, and is corrected by recumbency or by elevation of the diaphragm as produced by full expiration. The relatively common occurrence of inversion of the T wave in Lead II and its improvement with changes in position must be recognized in order to avoid an erroneous diagnosis of heart disease. Hence, when doubt exists tracings should be taken before and after exercise, full

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expiration, or tilting. Atropine also produces elevation of the T wave. In addition, increased amplitude and peaked P and T waves may be noted occasionally. ST elevations in Leads II and III are not uncommonly seen but they are not coved (Figure 1). Serial changes resembling coronary disease or myocarditis are never noted.

ST and T wave changes which may occur in the electrocardiogram during the course of the hyperventilation syndrome are occasionally marked and may be confused with those of myocardial infarction (see Figure 1). It is believed that these are due to changes in the pH of the blood toward the alkaline side, since alkalosis induced by other means may cause similar alterations in the electrocardiogram.

Acute Nonspecific Myocarditis

A commonly neglected aspect of heart disease is damage caused directly by systemic infections. Unfortunately, this is not recognized often enough because the primary disease may predominate the clinical picture, etiologic

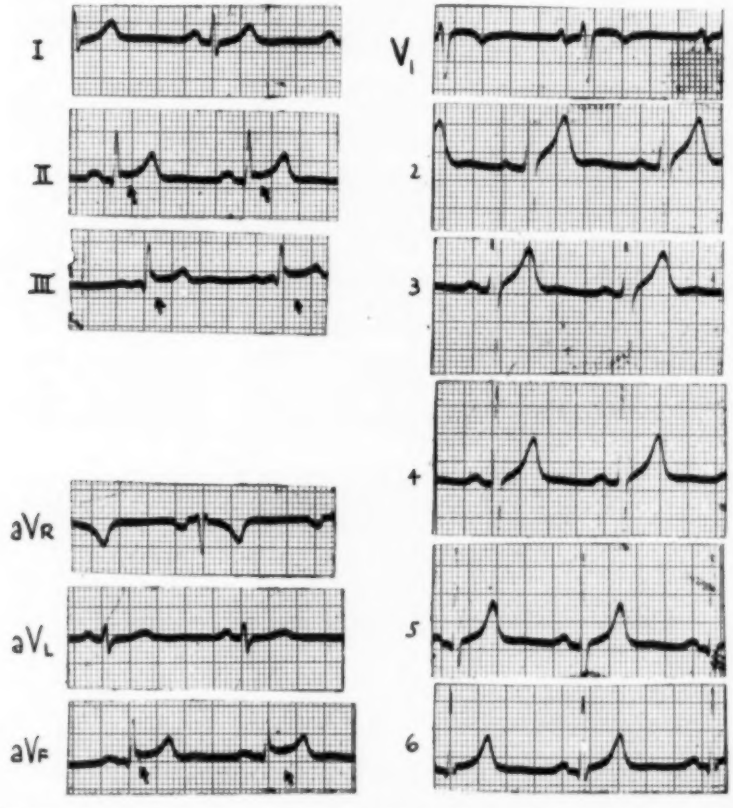

FIGURE 1: *Neurocirculatory Asthenia.* White male, age 36. Blood pressure 102/80. Note ST elevation in Leads II, III, aVF.

factors remain unidentified, confusion persists between toxic myocarditis and acute infectious myocarditis, and finally, the clinical and electrocardiographic manifestations occur in atypical and unanticipated forms.

The appearance of cardiac symptoms and signs following an acute infectious disease, whether of bacterial, rickettsial or viral origin, is highly significant. Dyspnea, angina, palpitation, gallop rhythm, arrhythmias, murmurs, cardiac enlargement and eventually myocardial insufficiency are most significant.

Electrocardiographic changes afford the most definitive evidence in establishing the diagnosis. Alterations may not be evident in every case and may not be continually positive in every instance. Therefore, it is

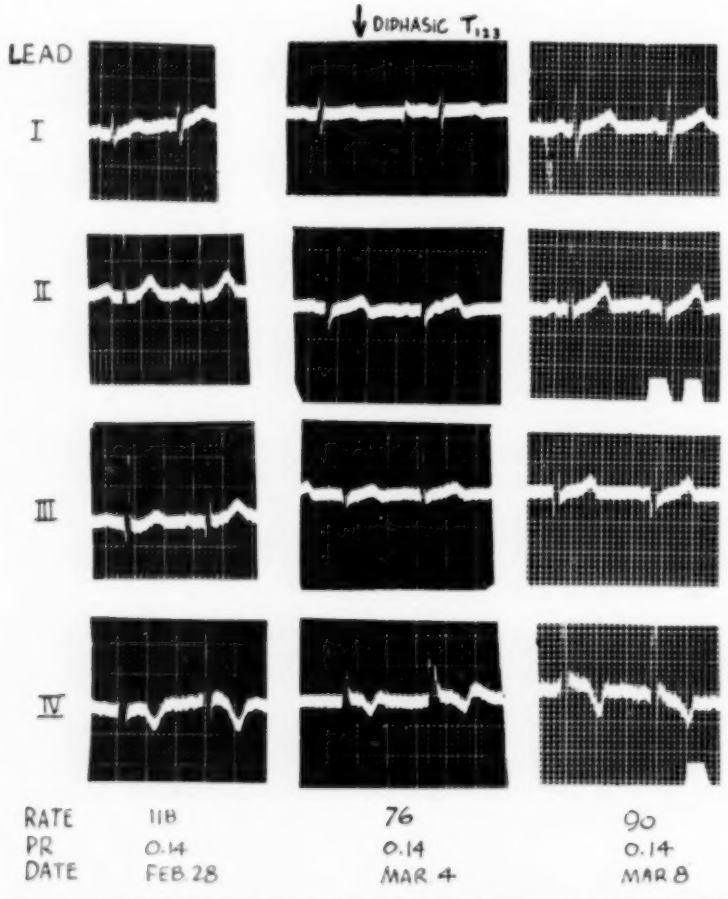

FIGURE 2: QRS and T wave changes suggestive of acute infectious myocarditis (non-specific) complicating primary atypical pneumonia in a five year old male. Sudden onset of precordial pain, increased breathlessness, palpitation, weakness first apical sound followed by asthenia and persistently elevated sedimentation rate. These changes occurred during the stage of pneumonic resolution.

important to perform serial studies. A constantly changing electrocardiogram is the most diagnostic of all the findings (Figure 2). The abnormalities usually disappear with the subsidence of the acute infectious process. Any of the following changes suggestive of myocardial disease may be present:

a) Increased P-R interval (with varying degrees of heart block).
b) Arrhythmias: sinus tachycardia, paroxysmal tachycardia, auricular fibrillation (late).
c) T wave inversion (Figure 3).
d) ST segment changes.
e) Low amplitude and slurring of the QRS complexes.
f) Bundle branch block.

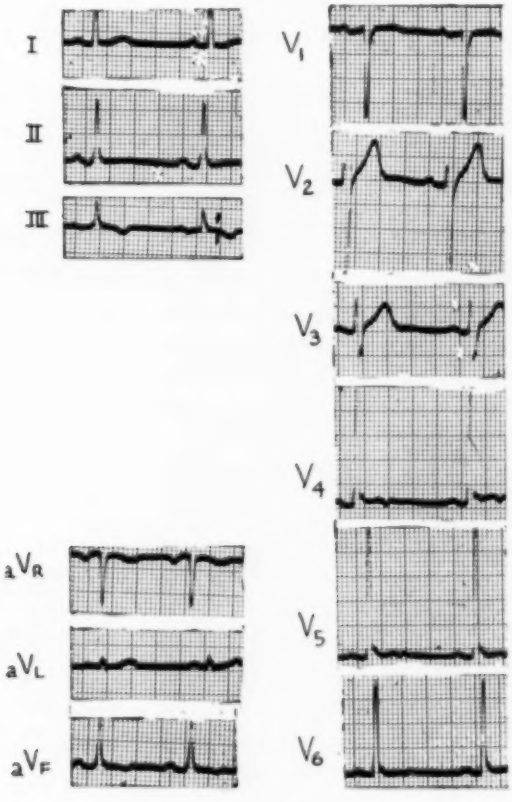

FIGURE 3: *Acute Nonspecific Myocarditis* following acute infectious mononucleosis in a 23 year old white male. Note low notched T wave in Lead II and inversion Lead III. Polyphasic T wave in V_1-V_6. (Reich, N. E.: The Uncommon Heart Diseases, Springfield, Illinois, C. C. Thomas, 1954.)

Acute Nonspecific Pericarditis

This is a benign disease of obscure etiology that has a predilection for young males, is frequently characterized by numerous recurrences, and is usually preceded by a history of upper respiratory infection.

The clinical picture is one of severe chest pain or discomfort, dyspnea, fever, and pericardial friction rub usually persisting for one day. Blood studies reveal increased sedimentation rate and leucocytosis. Aspiration shows clear or cloudy fluid. X-ray films, angiocardiography,, and kymography may be helpful when there is sufficient hydropericardium.

Electrocardiographic manifestations of pericarditis are due to subepicardial myocarditis, although myocardial anoxia and biochemical changes following epicardial irritation have also been implicated.

The pattern is sufficiently distinctive to permit the diagnosis to be made even in the absence of other findings.

The essential components are the elevation of the RST segments with dome-shaped or peaked T waves. The evolution of the entire pattern with

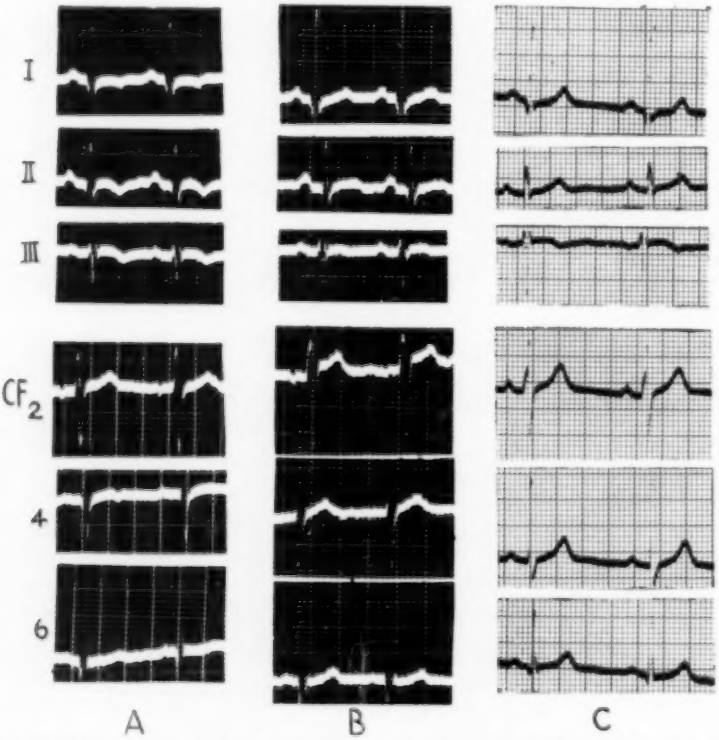

FIGURE 4: *Acute Nonspecific Pericarditis.* (A) A 24 year old white soldier with severe primary atypical pneumonia. X-ray films showed marked pericardial effusion for three weeks. EKG reveals negative T waves due to subepicardial myocarditis accompanying pericarditis.—(B) T waves becoming upright two months later. (C) Normal electrocardiogram six years later.

reversion to normal ordinarily takes place in a matter of weeks. There is no depression of the RST segment at any time; the T waves never show a classic reciprocal relationship in Leads I and III; no Q pattern ever develops in the standard or chest leads as they do in myocardial infarction; and the RT elevations are usually less marked and of much longer duration than in acute infarction. The same changes may take place in the chest leads and in the unipolar leads from the left arm (aVL) and the left leg (aVF). The T waves may reverse to the opposite direction (Figure 4).

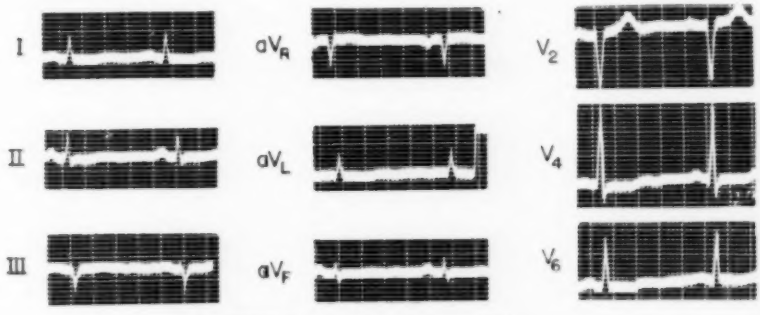

FIGURE 5: *Myxedema Heart Disease.*

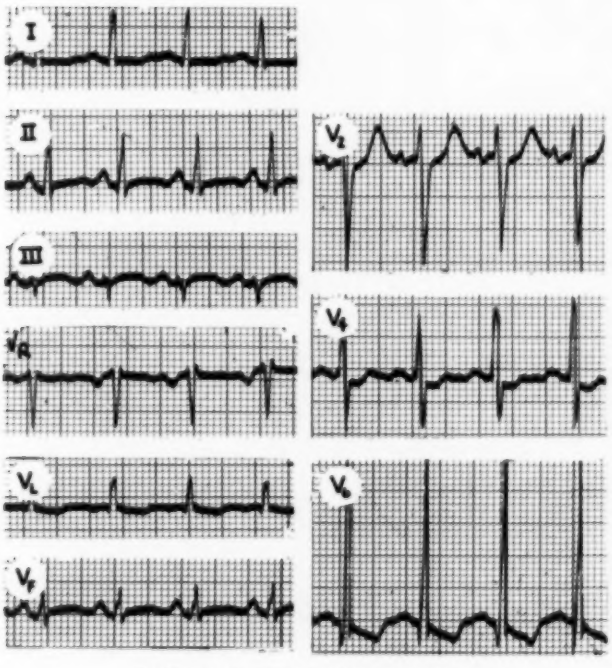

FIGURE 6: *Beriberi Heart Disease.*

Chronic Constrictive Pericarditis

Recognition of this condition is imperative because of complete surgical restitution today. The etiologic factor remains undiscovered in most instances in spite of careful history and search for organisms. Rheumatic fever, pleuropulmonary infections including tuberculosis, and myocardial infarctions are important causes. It consists of an inflammatory lesion of the pericardium and epicardium in which the fibrous adhesions, often associated with calcific deposits or encapsulated fluid, contract around the heart. Hence, the signs are basically those of cardiac constriction or fixation. Eventually, interference with diastolic filling and systolic con-

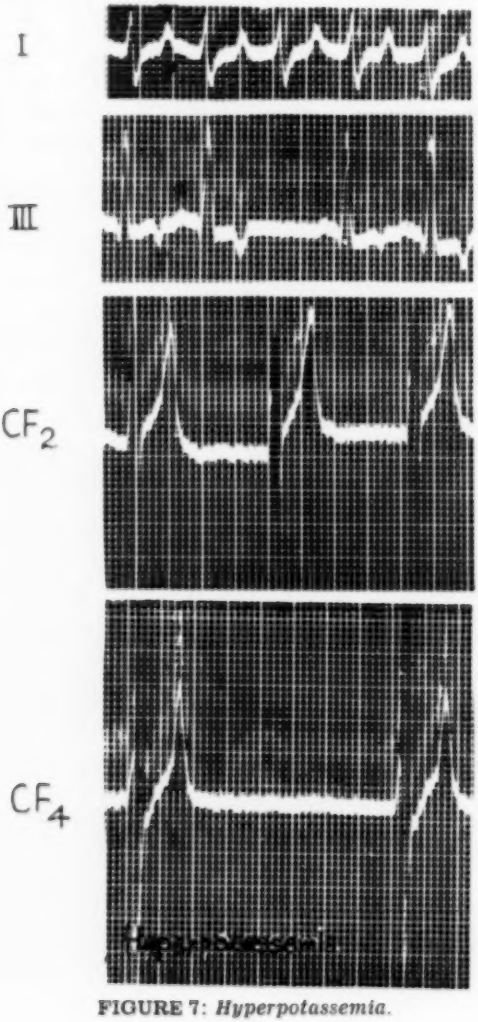

FIGURE 7: *Hyperpotassemia.*

traction results in right heart failure syndrome. Circulation time, venous pressure, and various types of x-ray studies (including fluoroscopy, electrokymography and roentgenkymography) reveal generalized or localized diminution in the pulsation pattern.

The electrocardiogram is always abnormal. In fact, the changes may show surprising uniformity.

a) T waves are low or inverted, usually in all standard and left chest leads.
b) QRS complexes are of low voltage in the standard leads.
c) Auricular fibrillation occurs late in the disease.
d) Fixation of the electrical axis, even though the body position is changed.

Thyrotoxic Heart Disease

Cardiovascular involvement during hyperthyroid states ranges from simple physiologic overactivity to severe organic changes, such as marked enlargement and congestive failure. Hence, the course of thyrotoxic heart disease is variable, depending on the age of the patient, and severity and duration of the intoxication. Cardiovascular symptoms are palpitation, vague chest pains, and dyspnea. Signs include forceful pulsations, bruit over the thyroid, harsh systolic murmur over the third left interspace probably due to increased pulmonary circulation; wide pulse pressure, and eventually cardiac enlargement. Circulation times, tracer tests, blood iodine levels and fluorocardiography are most helpful but a simple BMR is usually sufficient to establish the primary diagnosis in the absence of heart failure.

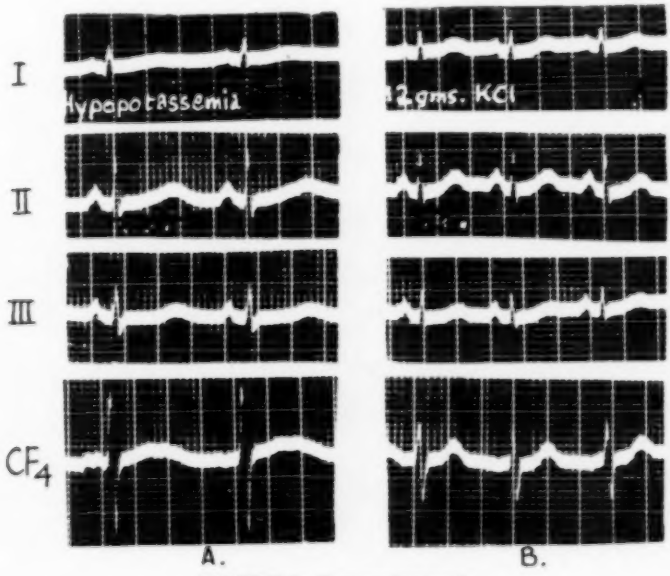

FIGURE 8: *Hypopotassemia.*

Electrocardiographic tracings are not diagnostic. The arrhythmias include extrasystoles, auricular fibrillation or flutter, auricular paroxysmal tachycardia and partial AV block. Low or inverted T waves, especially in Lead II, are attributed to sympatheticotonia. More rarely, the T waves may appear tall and rounded or pointed. Left ventricular strain pattern becomes evident in long-standing cases.

Myxedema Heart Disease

Underactivity of the thyroid gland eventually produces cardiac dysfunction as a result of myxedematous changes. This occurs in approximately three-fourths of untreated cases. The disease occurs at any age and has no sex predominance. Symptoms and signs first appear when sudden demands are made upon the decreased cardiac reserve. Dyspnea, precordial pain, bradycardia, cardiac enlargement and sluggish heart sounds may appear. Roentgenograms may show a great and diffuse increase in heart size. Fluoroscopy, kymography and electrofluorocardiography show mark-

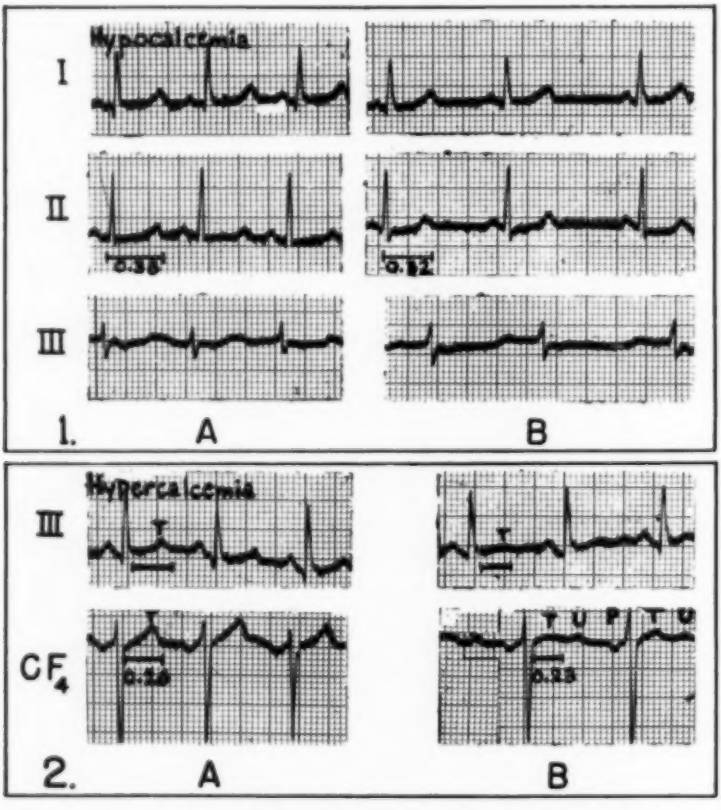

FIGURE 9: *Hypocalcemia and Hypercalcemia.* (From Reich, N. E.: The Uncommon Heart Diseases, Springfield, Illinois, C. C. Thomas, in press.)

edly decreased pulsations despite the increase heart size. Therapeutic response to specific therapy is striking and diagnostic. The heart shadow shows a striking diminution in size and increased amplitude of excursion during an interval of weeks.

Electrocardiograms are fairly characteristic (Figure 5). Sinus bradycardia, low voltage QRS complexes, and absence or inversion of T waves in the standard and chest leads are pathognomonic. There may be varying degrees of AV heart block. These findings return to normal with thyroid therapy.

Beriberi Heart Disease

Vitamins are indispensable substances necessary for proper nourishment of individual cells and for catalysis of vital cellular processes. Although the demand is for small amounts, they must be obtained entirely from exogenous sources. Cardiovascular disturbances are sometimes an important feature of these deficiencies, especially with thiamin chloride. Recent literature has made it increasingly evident that the syndrome of "beriberi heart" is subject to great variation in clinical manifestations, pathology and course.

In fact, confusion with thyrotoxic heart disease, neurocirculatory asthenia and acute nonspecific myocarditis is not uncommon.

The diagnosis of beriberi heart disease rests on singularly few stalwart criteria. The following features are considered essential before the presence of beriberi heart disease can be established: (1) enlarged heart with sinus rhythm; (2) dependent edema; (3) elevated venous pressure; (4) nonspecific electrocardiographic changes; (5) history of three or more months of a diet deficient in thiamin; (6) signs of neuritis or pellagra; (7) absence of all other causes of heart disease; (8) therapeutic test with clinical recovery and return of heart size and electrocardiogram to normal.

Electrocardiogram (Figure 6) commonly reveals the following four abnormalities:

a) Bradycardia (occasionally tachycardia).
b) Low voltage QRS complexes.
c) Inverted T waves, especially in chest leads.
d) Prolongation of electrical systole (QT interval).

The administration of thiamin chloride characteristically results in prompt return to normal and, hence, aids in the differentiation from hypothyroidism which produces a somewhat similar electrocardiographic and x-ray picture.

Electrolytes and the Heart

The classic experiments of Ringer in 1883 concerning the importance of electrolytes in cardiac physiology still form the basis for our present knowledge of electrolyte in balances. He observed that sodium chloride perfusate in the frog's heart maintained cardiac contractions for only a few beats with cessation in diastole. The addition of calcium restored the contractions for a time but the heart finally came to a standstill in systole (calcium rigor). The addition of potassium antagonized the calcium effect,

restoring and maintaining the contractions. However, an excess of potassium resulted in full relaxation of the heart in diastole (potassium inhibition).

Since then, numerous investigators have endeavored to discover the physiological importance of the various electrolytes in many types of clinical conditions. The advent of the flame photometer has greatly accelerated studies during the past decade. It is only in recent years that clinical and electrocardiographic applications of Ringer's fundamental observations have been possible. In fact, the electrocardiogram has become a valuable tool in the recognition of individual electrolyte imbalances.

Hyperpotassemia

Many clinical conditions are associated with hyperpotassemia. These include states in which potassium excretion is decreased by renal insufficiency such as that caused by parenchymal kidney disease, urinary obstruction, sulfonamide anuria, Addison's disease, and severe dehydration; or the release of large amounts of potassium from intracellular sources, such as occurs in massive hemolysis of red blood cells or severe hemorrhage, and in extensive necrosis of tissue following trauma, the crush syndrome, or burns.

Patients may become weak and stuporous and develop rapid shallow respirations due to paralysis of respiratory muscles. Finally, flaccid paralysis of voluntary muscles appears. Deglutition may become difficult and complicate therapy.

The electrocardiogram serves as a fairly good criterion of serum potassium levels because of the parallel changes in serum concentration and electrocardiographic alterations. The earliest electrocardiographic changes observed in man are elevated and peaked T waves (Figure 7). As serum potassium level rises, an increased PR interval is noted which may be followed by auricular standstill. Obliteration of the ST segment with the T wave originating from the S wave is noted progressively. With still higher serum potassium levels, widening of the QRS complex occurs and a biphasic ventricular complex may be seen. Death finally occurs as a result of cardiac arrest or ventricular fibrillation.

Hypopotassemia

Studies on familial periodic paralysis and diabetic acidosis have contributed toward the correlation of electrocardiographic changes and hypopotassemia. Other clinical conditions associated with low plasma potassium are postoperative states, the cell building phase which follows massive tissue destruction, the ion readjustment phase following recovery from the loss of fluid containing electrolytes (diarrhea, draining fistula, gastric suction, and repeated use of mercurial diuretics), sprue, and DOCA in large doses.

The clinical picture of potassium depletion consists of muscular weakness, partial respiratory paralysis, waterhammer pulse with irregular rhythm, increased pulse pressure, cardiac dilatation with systolic murmur, and

increased venous pressure. Symptoms disappear after administration of potassium.

Electrocardiographic alterations (Figure 8) include prolongation of the QT and PR intervals, flattening or inversion of T waves, depression of the ST segment, decrease in the amplitude of the QRS complexes, intraventricular block, or the occasional appearance of prominent U waves due to myocardial irritability. Although these changes may occur in various combinations, the most constant disturbance is prolonged QT interval.

Hypercalcemia

More or less constant hypercalcemia may be seen in such conditions as hyperparathyroidism, Boeck's sarcoid, hypervitaminosis D, and carcinoma of the breast with osseous metastases. Shortening of the QT interval at the expense of the ST segment is the most constant feature (Figure 9). Prolongation of the PR interval and slightly slurred QRS complexes are inconstant features.

Hypocalcemia

Tetany and electrocardiographic changes have been reported in patients who have borderline calcium deficiency which is further reduced below the critical level by excessive diuresis caused by mercurial diuretics, purines, coffee and diabetes. In hypocalcemic states such as occur in hypoparathyroidism, acute pancreatitis, sprue and uremia, the electrocardiogram characteristically shows prolongation of the QT interval. This differs from the QT prolongation of hypopotassemia which ensues as a result of rounding and broadening of the T wave. In hypocalcemia, the duration of the PR intervals and QRS complexes is not increased, the RST segments remain isoelectric, and the T waves are not altered in contour, amplitude or duration. Prominent U waves do not occur (Figure 9).

SUMMARY

Non-diagnostic electrocardiographic tracings are encountered frequently which do not coincide with the criteria of established picture. They are occasionally confused with more characteristic patterns. Such variations which are included in this discussion are found in neurocirculatory asthenia, acute nonspecific myocarditis or pericarditis, chronic constrictive pericarditis, thyroid dysfunctions, beriberi, and various electrolyte imbalances.

Recognition of suggestive patterns in conjunction with a careful history, examination, and other laboratory studies may prove vital since most of these conditions are reversible with appropriate therapy.

RESUMEN

Se encuentran trazos no diagnósticos frecuentemente que no coinciden con el criterio del cuadro establecido. Se confunden ocasionalmente con cuadros más característicos. Tales variaciones como las incluidas en esta discusión, se encuentran en astenia neurocirculatoria, pericarditis crónica

constrictiva, disfunción de tiroides, beriberi y varios desbalances electrolíticos.

Es vital el reconocimiento de los cuadros sugestivos en conjunción con una historia quidadosa, examen físico y otros estudios de la boratorio ya que la mayoría de estas alteraciones son reversibles con el tratamiento adecuado.

RESUME

On peut rencontrer couvent certains tracés électrocardiographiques qui ne correspondent pas aux aspects bien connus. Parfois on les confond avec des images plus caractéristiques. L'auteur étudie ces altérations, que l'on peut trouver dans l'asthénie neurocirculatoire, dans les myocardites ou les péricardites aigues non spécifiques, dans les péricardites constrictives chroniques, dans les troubles de la fonction thyroïdienne, dans le béri-béri et dans certains déséquilibres des électroylte.

Il est capital de reconnaitre les tracés en les associant à l'étude attentive de l'histoire du malade, à l'examen clinique et aux autres épreuves de laboratoire. Cette étude est d'autant plus importante que les anomalies que l'auteur rapporte peuvent disparaitre sous l'influence d'une thérapeutique convenable.

The Practical Value of Electrocardiography

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Electrocardiography, a graphic method of investigation of the heart, had such a rapid development that periodic evaluations of its practical usefulness are necessary. Overemphasis by enthusiastic workers may stress the value of this method beyond its actual possibilities; this may cause deceptions or diagnostic errors, or simply prevent the use of other, more appropriate, methods of investigation. On the other hand, underemphasis by a few die-hard old timers, misuse by poorly trained workers, or disappointment in its findings, occasionally cause unwarranted criticisms. It is appropriate to say that, in the presence of wide enthusiasm, criticisms are usually limited to personal comments and seldom find their way into medical literature.

Electrocardiographic technique is now established on a generally standardized basis. This consists of the use of 12 leads (three standard limb leads, three augmented V-leads of the limbs, and six precordial V-leads). Additional chest, esophageal, or epigastric leads, as well as functional tests, are sometimes necessary.

An *electrocardiographic report* can be of different types: (1) purely descriptive; (2) including analysis of certain peculiarities like axis deviation, premature beats, etc.; (3) including a diagnosis such as "atrial flutter," and "myocardial infarction" or "digitalis heart".

Complete electrocardiographic evaluation can be done only by a cardiologist who has examined the patient. The study of multiple precordial leads emphasizes the need of close supervision of the technician.

It is impossible to draw a sharp line between normal and abnormal tracings. In reaching a decision, the observer must consider the possible occurrence of a certain variation in the ecg of a normal person. Personal experience and additional clinical and laboratory data determine whether an abnormality should be considered pathologic.

The electrocardiogram can be used for "timing" certain accidents or waves recorded by means of mechanical, sound, or roentgenological methods. Thus, a venous tracing, a phonocardiogram, or an electrokymogram, can be recorded together with an electrocardiogram.

An electrocardiogram gives accurate information about *the pacemaker of the heart* and permits evaluation of the atrial and ventricular rates. Thus, the ectopic rhythms are easily studied.

Rhythms by usurpation are those where an ectopic focus with high excitability becomes the pacemaker *(atrial and nodal tachycardia, atrial flutter, ventricular tachycardia, atrial fibrillation, premature contractions,* and also *ventricular flutter and fibrillation). Rhythms by default* are those where lack of a normal sinus impulse or interruption in its transmission

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require control of the heart by a new, lower pacemaker *(nodal rhythm* and *idioventricular rhythm* due to sinus arrest, paralysis, or depression; to block; or to a-v block).

The study of the *electric axis* of the heart has attracted considerable attention since Einthoven. Even though there cannot be exact identification of the electrical with the anatomical position of the heart, displacements and rotations of this organ caused by either mechanical phenomena (traction, compression) or sectional enlargement (dilatation or hypertrophy of one ventricle), are accompanied by remarkable modifications of the electric axis. Thus, study of this axis can supply *indirect* data in valvular defects, congenital malformation, hypertensive heart disease, and cor pulmonale. The most striking changes are those caused by *dextrocardia*.

The study of the V-leads, developed as a consequence of Wilson's and Goldberger's investigations, has increased the accuracy of determination of the position of the heart.

Small changes in the duration of QRS, modifications of its shape, secondary changes of the T wave, concurrent modifications of the axis, and comparison of V_1-V_2 with V_5-V_6, permit identification of the following lesions of either ventricle: *ventricular hypertrophy* and *"strain"; bundle branch block; intraventricular block*.

A delay of a-v conduction (determination of P-R); changes in the duration of electrical systole (determination of Q-T); and evidence of increased excitability (premature contractions, paroxysmal tachycardia), reveal diffuse myocardial disturbance. This is typical of acute *myocarditis*, as well as of *coronary occlusion*.

Changes of the metabolism, electrolyte imbalance, and effect of digitalis or quinidine on the myocardium, are also revealed by electrocardiography.

Changes of the *coronary circulation* are not directly revealed by the electrocardiogram. However, the repercussion of decrease in the supply of blood (and oxygen) to the myocardium is such that the electric tracing is very revealing. Three different stages may occur in the evolution of a transmural myocardial lesion due to coronary disturbance. They are revealed by three patterns: (a) *pattern of ischemia* (inverted T wave) due to predominant delay of repolarization of the subepicardial layers; (b) *pattern of injury* (raised S-T) due to predominant suffering of subepicardial layers; (c) *pattern of necrosis* (QS or QR complex followed by inverted T) due to electrical inertia of the tissue. It should be emphasized that the type and course of evolution of the tracings is even more important than the changes themselves. Therefore, repeated tracings should be recorded.

Alterations of the electrocardiogram in *pericarditis* consist of three main patterns: (a) *pattern of ischemia* (inversion of the T wave); (b) *pattern of injury* (raised S-T); (c) *pattern of effusion* (low voltage). The two first patterns are due to an inflammatory process of the subepicardial layers; their interpretation is similar to that of similar patterns in coronary heart disease. The last pattern occurs only in large effusions and is due to short circuiting of electric potentials by the fluid.

Certain informative data are valuable in the interpretation of a tracing and in the writing of a report. They are: age and sex, blood pressure, valvular defects, drugs received, and clinical diagnosis.

In several diseases, the information supplied by the electrocardiogram is inadequate and may even be misleading. Knowledge of this may be useful and point out the need for different methods of study.

SUMMARY

The electrocardiogram has a unique place and can supply data even when symptoms and signs of heart disease are minor or absent. On the other hand, the connection between electric and mechanical phenomena of the heart is only indirect. Therefore, the data supplied by the electrocardiograph in valvular lesion, malformations of the heart, hypertension, and aortic or pulmonic lesions, are of limited importance. Excessive stress on minor modifications of the electric tracing in cases where sound or pulse tracings, roentgenology, or catheterization, give essential data, would only result in incomplete or incorrect diagnosis. A French proverb says: "La plus belle femme du monde ne peût donner que ce qu'elle a." Which means: "do not ask for a ready made diagnosis, supplied by the electrocardiogram."

RESUME

El electrocardiograma tiene un lugar singular y puede dar datos aún cuando los síntomas y signos de afección cardiaca son menores o faltan. Por otra parte, la conección entre los fenómenos eléctricos y los mechánicos es sólo indirecta. Por tanto, los datos proporcionados por el electro en la lesión valvular, las malformaciones del corazón, y las lesiones de la pulmonar y aórticas son de importancia limitada. La excesiva importancia dada a modificaciones menores del trazo eléctrico en casos en que la auscultación o los trazos esfigmométricos, la roentgenologia y la caterización dan datos esenciales, conduciria sólo a un diagnóstico incorrecto o incompleto. Un proverbio francés dice: "La mujer más bella del mundo no puede dar sino lo que ella tiene," lo que significa: "No se pida un diagnóstico ya hecho al electrocardiograma."

RESUME

L'électrocardiogramme à une place essentielle, et peut donner des résultats déterminants, même quand les symptômes et les signes de l'affection cardiaque sont discrets ou absents. Mais à l'opposé, les rapports qui unissent les phénomènes cardiaques électriques et mécaniques ne sont qu'indirects. Il en résulte que les informations apportées par l'électrocardiographie dans les lésions valvulaires, dans les malformations cardiaques, dans l'hypertension, dans les atteintes de l'aorte ou de l'artère pulmonaire, sont de valeur limitée. Il faut se garder de se baser d'une façon excessive sur des modifications discrètes du tracé électrique alors que les tracés du pouls ou des bruits cardiaques, la radiologie ou le cathétérisme donnent des conclusions formelles. Méconnaitre ce principe entrainerait des diagnostics incomplets ou incorrects. Un proverbe français dit que "la plus belle femme du monde ne peut donner que ce qu'elle a." Ceci signifie qu'il ne faut pas demander à l'électrocardiogramme un diagnostic tout fait.

Clinical Evaluation of Toryn, A New Synthetic Cough Depressant*

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The synthetic compound, bis - [1 - (carbo - B - diethyl - aminoethoxy) - 1 - phenyl-cyclopentane]-ethane disulfonate ("Toryn")† was found to depress the cough reflex.[1-3] It was thought not to have addictive properties nor to produce drowsiness.[1] Previous investigations of this drug lacked control and comparative observations. It is the purpose of this study to determine if toryn affords relief from chronic, severe, disabling cough and to compare its effectiveness with that of established anodyne drugs.

Material and Methods

Twenty-six patients were selected on the basis of severe, irritating, chronic cough as the presenting complaint. Those were excluded who had predominantly productive cough and especially if there was evidence of retention of secretions. Only those who gave promise of cooperation and some ability of self-observation were accepted. With few exceptions they had pulmonary disease of long standing with advanced organic pulmonary changes demonstrated by roentgenograms. All were partially or totally disabled by their disease and much disturbed by their cough. Eighteen (Nos. 1-18) were followed in the Medical Thoracic Clinic of a general hospital, while the remaining eight (Nos. 19-26) were bed patients in a sanatorium. The clinical characteristics are enumerated in Table I.

Physical and roentgenographic examinations, as well as routine blood and urine analyses were obtained before the study commenced and at intervals thereafter. All were seen at least once a week.

The following four drugs were compared, being dispensed as compressed white tablets of identical size and shape:

Placebo:	
Codeine sulfate	16.2 mg.
Dihydrocodeinone bitartrate	5 mg.
Toryn	10 mg.

The identity of the tablets was unknown to all physicians, nurses, and patients who took part in this study and remained unknown until after the data had been tabulated and analyzed at the conclusion of the inves-

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†Trade name of Smith, Kline and French Laboratories who provided the material for this study.

tigation. The dosage for each drug was one tablet after each meal. Administration of the third tablet was delayed until bed time in some patients with disturbing nocturnal cough. Each preparation was administered for one week. To out-patients the tablets were dispensed in the calculated amount in identical containers which were collected at the end of each week. The sequence of drugs was varied from patient to patient. All antitussive or expectorant agents taken prior to the study were discontinued, but patients accustomed to postural drainage were encouraged to continue this procedure.

The results of therapy were evaluated (1) by daily report cards on which the patients recorded their observations regarding cough and sputum at the end of each day, and (2) by weekly evaluation by the physician, according to the method used by Gold and associates[4,5] for evaluation of xanthines and later of Khellin in the treatment of cardiac pain. The interval evaluation was recorded before collection of the daily report card. Particular attention was paid to frequency and severity of cough, incidence of paroxysms, nocturnal cough and change in sputum. Patients were asked specifically about gastrointestinal disturbances, sleep, drowsiness and dizziness. The quantity of sputum of the hospitalized tuberculous patients was measured, while the amount of expectoration of the ambulatory patients was estimated.

Results

Twenty of the 26 patients selected for study completed the full course consisting of four consecutive weeks of one week on each drug. Two of these 20 (Nos. 9 and 15) lost one or more of the weekly report cards. Of the remaining six, five (Nos. 2, 3, 4, 8, 10) took two or more drugs for a full week but defaulted on the others. One with far advanced tuberculosis (No. 25) who had previously found some relief with 10 mg. of didhydrocodeinone bitartrate, refused each medication in turn when he failed to obtain satisfactory relief on the first day of administration. This patient is not included in the tabulations.

Cough During Administration of Toryn: The effect of toryn on the cough of individual patients is shown in Table I. The effects of placebo, toryn, codeine and dihydrocodeinone, as evaluated by the physician at weekly intervals, are summarized in Figure 1. Of 23 patients who took toryn for one week, 10 noted no effect, six reported slight decrease in cough, five noted good supression of cough and two reported complete or almost complete suppression. Seven preferred toryn to both codeine and dihydrocodeinone. In general, toryn appeared more effective than placebo and less effective than either codeine or dihydrocodeinone, although more patients gave preference to toryn than to either codeine or dihydrocodeinone.

In Figure 2 the results of the patients' reports with respect to changes in cough are summarized by addition of individual results. Twenty-three who took toryn for an aggregate of 138 days noted decrease of cough on 59 days or 43 per cent of the days. During a similar period of administration

TABLE I

CLINICAL CHARACTERISTICS OF PATIENTS AND EFFECTS OF TORYN

Pt.	Age	Sex	DIAGNOSIS	Cough Improvement With Toryn
1	62	M	Emphysema, severe	marked
2	54	M	Bronchogenic Carcinoma, recurrent	none
3	69	M	Emphysema, moderate; bronchiectasis	moderate
4	47	M	Emphysema, moderate; bronchiectasis	(1)
5	42	M	Bronchiectasis; tuberc.; arrested	slight
6	52	M	Pneumonectomy, rt.; emphysema, lt.; bronchiect.	none
7	49	M	Emphysema, severe	moderate
8	46	F	Bronchitis, chronic; anxiety state	(1)
9	41	M	Tuberc., arrested; thoracoplasty, lt.; decort., rt.	none
10	33	M	Bronchitis, chronic	none
11	32	F	Boeck's Sarcoid	slight
12	45	M	Emphysema, moderate; fibrosis, moderate	moderate
13	47	F	Bronchiectasis, cylindrical	none
14	65	M	Bronchogenic carcinoma, advanced	moderate
15	61	M	Emphysema, moderate; bronchiectasis	moderate
16	44	M	Emphysema, severe; bronchiectasis	slight
17	69	M	Bronchiectasis	marked
18	24	F	Bronchitis, chronic; tuberc., old; pnpt.	none
19	44	M	Tuberc., far advanced; emphysema, severe	none
20	45	M	Tuberc., moderately adv.; pneumoperitoneum	slight
21	52	M	Tuberc., far adv.; subcostal plombage; duod. ulcer	none
22	58	F	Tuberc., far advanced; emphysema, moderate	slight
23	58	M	Tuberc., far adv.; lt. pneumonect. & th'pisty.	slight
24	42	M	Tuberc., far advanced	none
25	42	M	Tuberc., far adv.; emphysema; cor pulmonale	(1)
26	34	M	Tuberc., far advanced with empyema	none

L E G E N D

Pt. - patient.
(1) - did not take Toryn.
(2) - P: placebo.
T: Toryn, 10 mg. t.i.d.
C: codeine sulfate, 16.2 mg. t.i.d.
D: dihydrocodeinone bitartrate, 5 mg. t.i.d.
1: most effective drug.
2: 2nd in effectiveness, etc.
0: no effect.
-: data incomplete.

TABLE I (Continued)

CLINICAL CHARACTERISTICS OF PATIENTS AND EFFECTS OF TORYN

——SPUTUM—— Before Toryn	With Toryn	New Symptoms While Taking Toryn	Drugs in Order of Effectiveness (pts. opinion) (2) P	T	C	D
3 oz.	decr.	none	3	2	1	4
3 oz.	3 oz.	occ. nausea (also on P); nocturia	0	0	-	-
> 10 oz.	decr.	previous dizziness aggravated	-	1	2	0
5-8 oz.	...	...	-	-	2	1
< 1 oz.	sl. decr.	none	0	1	2	3
> 10 oz.	sl. decr.	none	1	0	2	2
3-6 oz.	sl. decr.	none	2	1	0	3
none	...	...	2	-	-	1
½-1 oz.	½-1 oz.	none	0	0	1	0
3 oz.	incr.	nausea and dizziness (also on C)	-	0	0	1
½ oz.	incr.	none	0	2	1	0
2 oz.	sl. decr.	mod. drowsiness (also on P,C,D)	2	1	2	2
8 oz.	8 oz.	none	3	4	1	2
> 10 oz.	decr.	none	3	2	0	1
6 oz.	decr.	"dopey", also on C and D	1	1	1	2
6 oz.	decr.	none	0	2	1	3
2 oz.	decr.	none	3	1	2	3
none	none	none	0	0	2	1
6 oz.	6 oz.	none	0	0	2	1
2-4 oz.	2-4 oz.	none	0	1	0	0
1 tsp.	½ tsp.	none	0	0	-	-
0-½ oz.	1 tsp.	1 day abd. pain and emesis (also on P)	2	1	0	0
2 oz.	1 oz.	none	2	3	1	4
12 oz.	0-12 oz.	none	0	0	1	2
4-6 oz.	...	...	-	-	-	-
8 oz.	10-12 oz.	none	0	3	2	1

L E G E N D

Pt. - patient.
(1) - did not take Toryn.
(2) - P: placebo.
T: Toryn, 10 mg. t.i.d.
C: codeine sulfate, 16.2 mg. t.i.d.
D: dihydrocodeinone bitartrate, 5 mg. t.i.d.
1: most effective drug.
2: 2nd in effectiveness, etc.
0: no effect.
-: data incomplete.

of placebo, cough was decreased on 31 per cent of the days while on codeine and dihydrocodeinone the percentages of days with less cough were 55 per cent and 54 per cent respectively.

Standard errors of the differences between the percentages of days with less cough for each of the four drugs were determined for the group of patients as a whole. From Table II it is seen that the difference between placebo and toryn was twice its standard error. Hence a true difference between the percentages is likely (the odds are 21:1), but cannot be considered established statistically. The differences between placebo and codeine, and between placebo and dihydrocodeinone are even less likely to be due to chance, being of the order of four times the standard error. No difference is evident between codeine and dihydrocodeinone. While taking toryn, a number of patients noted changes in the characteristics of the cough, described as "less deep," "less hacking," or "easier to raise," irrespective of whether the cough decreased or not.

Sputum During Administration of Toryn: During toryn administration measurements of the quantity of 24 hour sputa of the seven hospitalized tuberculous patients (Table I) revealed no change in three, a moderate decrease in three, and a moderate increase in one. In the remaining 17 taking toryn the amount of sputum was estimated to be unchanged in four, slightly decreased in four, moderately decreased in seven, and increased in two. A similar trend toward decrease in sputum was also evident with codeine and dihydrocodeinone. In the absence of accurate measurements our data do not allow further comparison of the effect of these drugs on the character and quantity of the sputum.

No patient showed clinical evidence of retained secretions.

Side Reactions and Toxicity of Toryn: Of 23 patients receiving toryn, 18 noted no new symptoms. One (Case 2) noted occasional nausea and nocturia; nausea was also experienced during the week of placebo. A second (Case 3) felt that toryn aggravated his chronic dizziness. A third (Case 10) complained of nausea and dizziness, present also while taking

TABLE II

Statistical Evaluation of Differences Between Placebo, Toryn, Codeine, and Dihydrocodeinone as Indicated by Percentage of Days on which Cough was Less than Usual

Drugs Compared	Difference in Percent of Days Improved	Standard Error of Difference	DIFFERENCE / Standard Error
Toryn vs. Placebo	11.5	5.8	2.0
Toryn vs. Codeine	12.2	6.1	2.0
Toryn vs. Dihydrocodeinone	11.2	6.0	1.9
Codeine vs. Placebo	23.7	6.0	4.0
Dihydrocodeinone vs. Placebo	22.7	5.9	3.8

codeine. A fourth (Case 12) noted moderate drowsiness which also accompanied codeine, dihydrocodeinone and placebo. A fifth (Case 15) felt "dopey" some of the time but noted this also with codeine and dihydrocodeinone. A sixth patient (Case 22) had abdominal pain and emesis on one day; a similar episode, lasting one day, occurred while she was taking placebo.

With the exception of dizziness and drowsiness the relation of these symptoms to toryn appears uncertain. None of these symptoms was severe and none necessitated omission of the drug. Constipation was not observed. There was no evidence of cardiovascular side effects. No significant change in physical, roentgenological and laboratory findings became evident during this study. There was no evidence of blood dyscrasia, although follow-up blood counts were not obtained in all cases.

Of 22 patients taking codeine, three noted dizziness, three felt sleepy, one reported anorexia and one vomited. Of 23 taking dihydrocodeinone, three reported sleepiness and one became constipated. While taking placebo, four of 22 complained of drowsiness, and one attributed a "sore stomach" to the medication.

In this study during which no patient took toryn for more than one week consecutively there was no evidence of addiction.

Additional Observations of Effects of Toryn: For further evaluation of

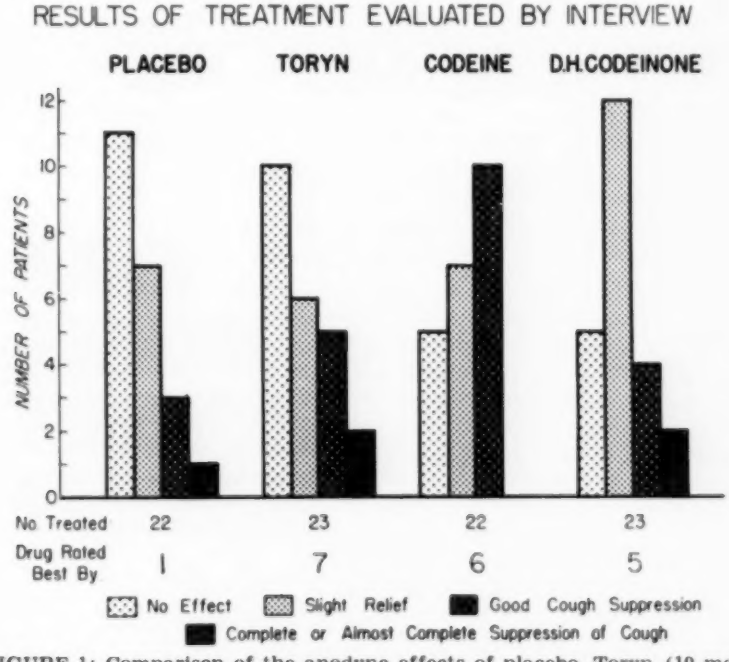

FIGURE 1: Comparison of the anodyne effects of placebo, Toryn (10 mg.), codeine (16.2 mg.), and dihydrocodeinone (5 mg.), as evaluated by weekly interviews of patients.

the problem of dizziness, the dosage of toryn was increased to 20 mg. three times a day. Ten were treated in this manner.

Of five ambulatory patients (Cases 6, 7, 14, 16, 17) four noted dizziness and drowsiness and one dreamt more than before; none had noted these effects while taking 10 mg. toryn three times a day. True vertigo was not observed. Toryn in double dose was effective in depressing cough in four patients, while one (Case 16), who had reported benefit from 10 my. toryn, observed no effect from the double dose.

The remaining five patients were hospitalized for far advanced pulmonary tuberculosis and had not received toryn previously. All had severe cough productive of at least one ounce of sputum daily. One complained of epigastric burning accompanied by nausea about two hours after medication, yet he was willing to complete his course of toryn, since he obtained partial relief. The second, a man with marked pulmonary fibrosis and cyanosis at rest, coughed less for about two hours after toryn; at the end of this period he vomited regularly until the drug was omitted at his request on the fourth day. The third and fourth patients noted no ill effects, but were uncertain as to the effectiveness of the drug. The fifth had a striking reaction which merits description:

J.M., a 44 year old man, with a total mixed empyema, on closed tube drainage, on the left and multiple cavities on the right, had been ill for 10 years and had required continuous nasal oxygen for the preceding nine months. Initial neurological examination had been negative and he was always rational. On the second day of administration of toryn his speech became thick and slurred, and he failed to recognize nurses and relatives. On the following day he became completely disoriented but remained quiet and without complaints. Neurological examination revealed disorientation as to time, place and person, hyperactive deep tendon reflexes and bilateral extensor plantar responses. He had periods of urinary in-

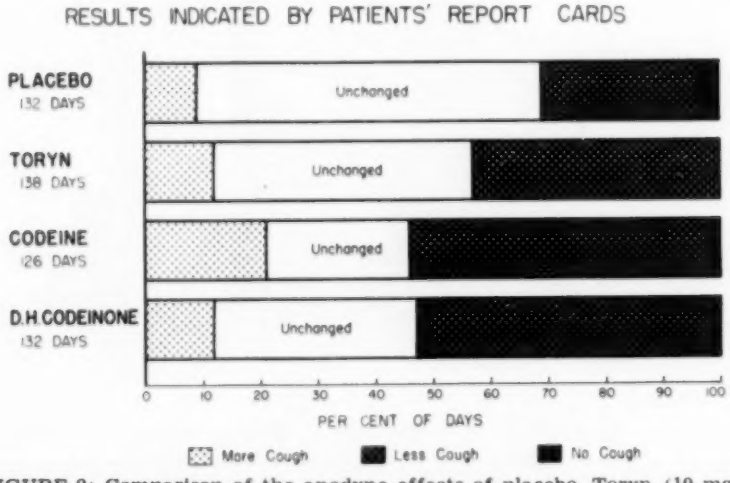

FIGURE 2: Comparison of the anodyne effects of placebo, Toryn (10 mg.), codeine (16.2 mg.), and dihydrocodeinone (5 mg.), as evaluated by pooling the patients' report cards.

continence. Twitching of the extremities was observed during his sleep. There was no evidence of respiratory depression, and no localizing signs were elicited. On the fourth day, Vitamin C was substituted for toryn. On the following day he became rational and continent, but his speech remained altered for two more days.

The possibility that this was an acute reaction to toryn cannot be ruled out.

The five hospitalized patients were also treated with placebo and double doses of codeine and dihydrocodeinone. The placebo was judged ineffective by all patients. Codeine sulfate and dihydrocodeinone each were considered superior to toryn by all patients, although one noted drowsiness and two others complained of moderate constipation while taking codeine.

Discussion

The present investigation was carried out to determine if the antitussive properties of toryn could be confirmed in a controlled study of patients with advanced pulmonary disease and severe cough.

The results indicate that some patients with severe chronic irritant cough found partial to considerable relief with toryn. With rather small doses, toryn takes a place in effectiveness between placebo on the one hand and codeine and dihydrocodeinone on the other. The patients selected represent the most difficult problems in management of cough, as demonstrated by the frequent failure of small doses of the two well established anodyne drugs to bring relief. There appeared to be no relationship between type of disease and relief by toryn. Like codeine and dihydrocodeinone, toryn may decrease the amount of sputum produced, presumably by its cough depressing action.

Although no patient with bronchial asthma was treated, a number with emphysema and some bronchospasm observed no decrease in wheezing or dyspnea on toryn. Patients with chest pain noted no analgesic action of toryn although depression of the cough reduced the pain on coughing. Toryn was not given long enough or in a manner suitable for evaluation of possible addictive properties.

Dizziness and drowsiness were the only reactions related to toryn 10 mg. thrice daily. When this dose was doubled, nausea was felt by two patients and was accompanied by vomiting in one. The incidence of dizziness and drowsiness increased in the ambulatory patients, and one developed evidence of a transient diffuse reaction of the central nervous system possibly related to toryn. It may be of significance that both the last-mentioned patient and the one who vomited so consistently after toryn were anoxic.

The high incidence of partial or even complete relief obtained with a placebo reaffirms the need for adequate controls in studies of effectiveness of drugs against symptoms even when dealing with advanced organic disease.

Further studies of toryn appear indicated to establish its mechanism of action and to define the conditions in which it is most effective. The nature of the dizziness also deserves further interest.

SUMMARY

1) Twenty-three patients with severe, chronic cough and underlying advanced organic broncho-pulmonary disease were given the new antitussive drug toryn in dosage of 10 mg. thrice daily for one week. This drug was compared to placebo, codeine sulfate, 16.2 mg., and dihydrocodeinone bitartrate, 5 mg., administered in identical manner, using the "double blind test".

2) Toryn was accompanied by partial to considerable relief from distressing cough in 57 per cent of patients, of which 54 per cent preferred toryn to codeine and dihydrocodeinone in the above dosage.

3) Drowsiness and dizziness appear to be side effects of toryn, especially upon administration of larger doses. Nausea was encountered in an occasional patient and may have been related to toryn, at least with the larger doses.

4) Toryn decreased the amount of sputum in 61 per cent of patients. There was no clinical evidence of retention of secretions.

5) When the percentage of days on which cough was decreased is compared, toryn takes its place between placebo on the one hand and codeine or dihydrocodeinone on the other.

RESUMEN

1) Se dió la nueva droga Toryn a la dosis de diez mg. tres veces al día, a veintitrés enfermos con tos severa, crónica, con avanzada enfermedad broncopulmonar. La droga fué comparada con substitutoneutro, con sulfato de codeína a la dosis de 16.2 mg. y con la dihidrocodeinona en bitartrato a la dosis de 5 mg. Todas estas substancias fueron administradas de idéntica manera, usando la "doble prueba ciega".

2) El uso de Toryn, fué seguido con una mejoría parcial o considerable de tos agobiante en cincuenta y siete por ciento de los enfermos, de los cuales cincuenta y cuatro por ciento prefirieron Toryn a la codeína y a la dihidrocodeinona en las dosis señaladas.

3) Somnolencia y mareo parecen ser los efectos colaterales del Toryn, especialmente cuando se administra en grandes dosis. Se observó náuseas en un enfermo, que puede atribuirse por lo menos a las grandes dosis de Toryn.

4) El Toryn hizo disminuir el esputo en el 61 por ciento de los enfermos. No hubo evidencia clínica de retención de secreciones.

5) Cuando se compara el porcentaje de días en los que la tos decreció, el Toryn se coloca entre el substituto neutro por un lado y la codeína y la dihidrocodeinona por el otro.

RESUME

1) 23 malades atteints de toux sévère chronique due à une affection organique bronchopulmonaire avancée, furent traités avec la nouvelle drogue, la "toryn" à la dose de 10 mmgr. trois fois par jour pendant une semaine. Ce produit est comparé avec des produits factices et avec le sulfate

de codéine, 16.2 mmgr. et le bitartrate dihydrocodéinone, 5 mmgr., administrés de manière identique.

2) La "toryn" produisit un soulagement partiel, mais considérable de la toux incoercible chez 57% des malades; 54% d'entre eux préfèrent la "toryn" à la codéine et au dihydrocodéinone selon la posologie indiquée ci-dessus.

3) Somnolence et vertiges semblent être les inconvénients de la "toryn", spécialement quand elle est administrée à de hautes doses. On nota des nausée chez un rare malade. On peut les mettre sur le compte du produit, au moins lors de son utilisation à des doses élevées.

4) La "toryn" diminua l'expectoration chez 61% des malades. Il n'y eut aucune manifestation clinique de rétention des sécrétions.

5) Quand on compare le pourcentage de jours pendant lesquels la toux diminua, on voit que la "toryn" prend place entre le produit factice d'une part, et d'autre part la codéine ou le dihydrocodéinone.

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Bronchographic Abnormalities in Alveolar Cell Carcinoma of the Lung*

A New Diagnostic Sign

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Previous reports have indicated that there are no pathognomonic roentgen signs of alveolar cell carcinoma or even of pulmonary adenomatosis. Neither routine chest films nor supplementary roentgen studies have thus far proved to be of value in establishing an unequivocal diagnosis in this disease.[2-6,8-10,13] Furthermore, the distinction between this type of carcinoma and the parenchymal changes of the ordinary bronchogenic variety can rarely be made. It should be noted at this point that the distinction between pulmonary adenomatosis and alveolar cell carcinoma is doubtful and for purposes of this discussion we will not attempt to make any sharp distinction between these two conditions although the cases herein reported are all considered to be alveolar cell carcinoma. It is our purpose to report bronchographic abnormalities which appear to be so characteristic that their presence should at least suggest the diagnosis of alveolar cell carcinoma. In the past decade there have been a number of thorough reviews of this disease.[12,14] We will therefore confine our remarks to those aspects that bear directly upon the bronchographic findings.

One of us (L.G.R.) noted an unusual bronchographic distortion in a bizarre pulmonary lesion encountered at the University of Minnesota Hospitals in 1935. At that time this was thought to represent the effect of a diffuse carcinomatous infiltration of the lung, so-called lymphangitis carcinoma, or possibly as a result of a diffuse infiltrating metastasis. In 1942, another such case was observed in which a similar bronchographic distortion of bizarre character was encountered. This, too, was reported as a diffuse carcinomatous infiltration of the lung. A review of the pathology in the latter case led to the conclusion that it was a form of epithelialization of the alveoli and it was so reported by Bell[1] in 1943. Incidental mention of the bronchographic abnormality was made in this report. A later review of the pathology in this case, in the light of subsequent studies, indicates that no doubt the process was really an alveolar cell carcinoma.

Our interest in the potentialities of bronchography in this entity was stimulated through a review of some of our cases of carcinoma of the lung in the summer of 1951. Another case of alveolar cell carcinoma in the lung, similar in many of its bronchographic aspects to the previously mentioned case, was encountered at that time. Since then four additional similar cases have come to our attention.

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The essential changes in the bronchographic pattern, as we have observed them, which should suggest the diagnosis of alveolar cell carcinoma of the lung are as follows: (1) a uniform, diffuse, rather marked narrowing of the segmental bronchi in the areas of lung involvement, (2) rigidity and elongation of the bronchi, (3) filling rather than coating of the bronchi, and (4) a lack of filling of the terminal ramifications of the bronchi (appearance of the "leafless tree"), or of the alveoli of the lung segments supplied by these bronchi.

Case Reports

Case 1: A 52-year old white female was admitted to the University of Minnesota Hospitals on September 7, 1935. About a year before she developed chills, fever and occasional chest pain. The attack cleared up within a short period of time. In December, 1934, she developed a cough and in May, 1935, chest pain, both of which persisted until the time of admission to this hospital. Physical examination of the chest revealed impaired resonance bilaterally with bronchovesicular and bronchial breathing.

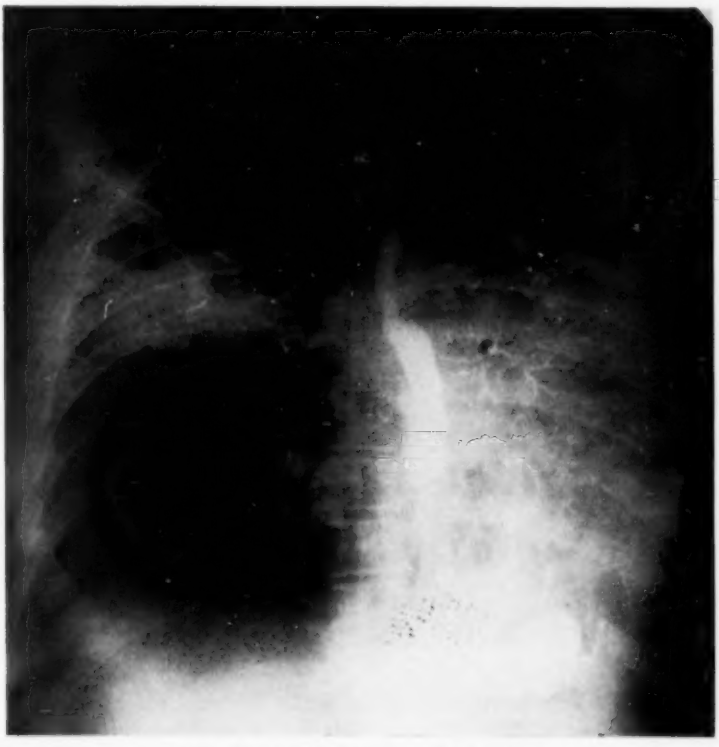

FIGURE 1 (Case 1): Extensive infiltration involving almost the entire left lung and a large portion of the right upper lobe. Bronchogram demonstrates the narrow, rigid, thread-like appearance of the smaller bronchi in the areas of involvement. There is no extension beyond the terminal bronchi into the lung parenchyma. The major bronchi are not well made out. Patient swallowed a large portion of the iodized oil, hence the shadow of the esophagus and stomach.

Repeated x-ray examinations showed an extensive process involving almost the entire left lung. On the right side there also appeared to be an extensive fibrotic and nodular process involving portions of the upper and middle lobes. The bronchogram revealed the findings exhibited in Figure 1. The bronchi are extremely narrow, elongated, rigid, and only the smaller bronchi appear to be filled with the contrast medium. There is little or no extension of the contrast into the alveoli. The whole appearance suggests that the bronchi are more or less uniformly encased by a thickening or infiltration of the surrounding lung parenchyma. A diagnosis of extensive carcinoma of the lung was made, possibly lymphangitis carcinoma or infiltrating metastasis. The patient expired on December 27, 1935.

Autopsy was performed and the diagnosis of diffuse carcinoma, primary in the lung, was confirmed. A recent review of these sections, however, proved this to be unequivocally an alveolar cell carcinoma of the lung, a diagnosis which was very infrequently considered in 1935.

Case 2: (Case previously reported by Dr. E. T. Bell[1]). A 63-year old white male was admitted on March 5, 1942. For a one and one-half year period prior to admission he had noted increasing exertional dyspnea. Cough which had begun two years prior to admission had become pronounced in the four months preceding his admission with the production of large amounts of clear, watery sputum. Infrequent hemoptysis and weight loss had also been noted in the months prior to entry into the hospital.

Examination of the chest revealed signs of consolidation over the posterior left mid-lung field. A few scattered rales were present over the right chest.

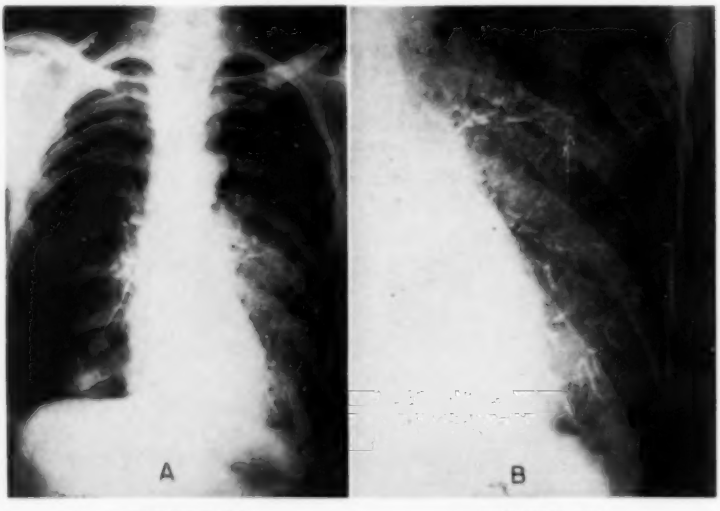

FIGURE 2A FIGURE 2B

Figure 2A (Case 2): Extensive infiltration in the left lower lobe and a small area of infiltration in the right lower. Bronchography shows identical findings as described above. The appearance of many somewhat irregular roentgen opaque threads running through the areas of involvement is well shown here.—*Figure 2B:* Detailed view of the left lower lobe shows the characteristic bronchographic picture seen with alveolar cell carcinoma. The bronchi of the third and fourth order are completely filled with the iodized oil but there is no extension beyond them into the bronchioles or parenchyma. They are rigid, extremely narrow and rather uniform in their size.

Roentgen examination of the chest showed an extensive density in the left lung and a less extensive density in the right middle lobe. A bronchogram was done (Figures 2A and 2B). The findings are almost identical with those described in Case 1. The curious appearance of many narrow bronchi, completely filled with

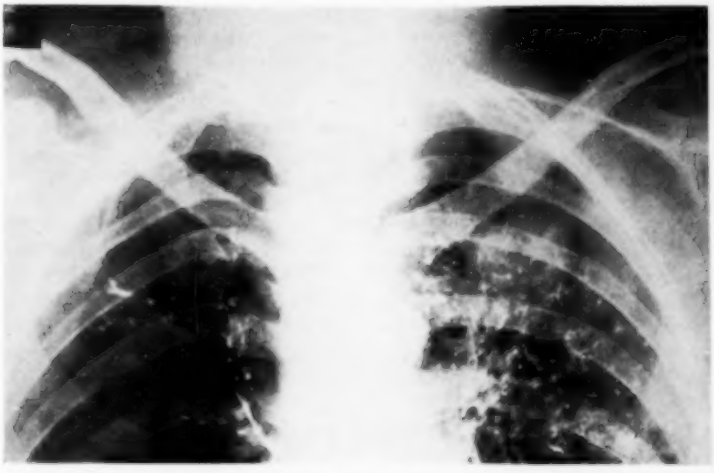

FIGURE 3 (Case 3): Alveolar cell carcinoma involving the left upper lobe alone with a nodular lesion. Bronchography shows almost identical findings as previously described, localized to the area of the involvement. Below this in the normal portions of the lung there is some extension of the contrast into the parenchyma.—

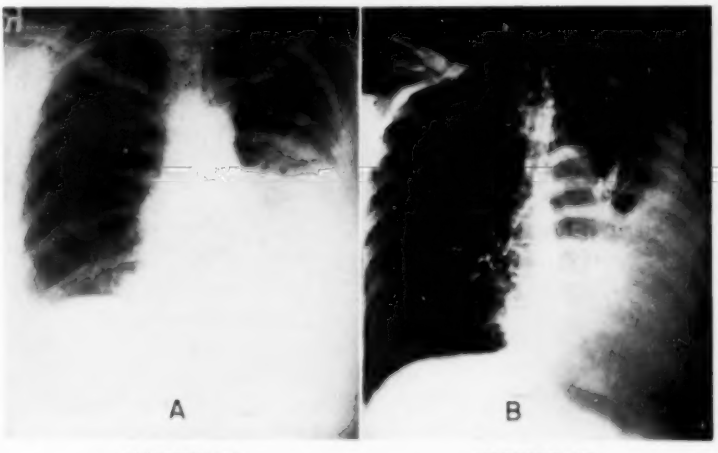

FIGURE 4A FIGURE 4B

Figure 4A (Case 4): Extensive infiltrative process in the left lung. There is a diffuse involvement at the base of the right lung also, although this is much less obvious.—*Figure 4B*: Bronchogram shows again the elongated, rigid, very narrow bronchi extending into the area of involvement. The appearance of bronchi which are diffusely surrounded by tumor tissue and compressed is well demonstrated here.

the contrast medium, and resembling roentgen opaque threads scattered throughout the lung, is well brought out. The diagnosis of an extensive infiltrating carcinoma of the lung was made and the patient was discharged.

The patient subsequently died elsewhere and lung sections reviewed here revealed diffuse epithelialization of the lung, later established as alveolar cell carcinoma.

Case 3: A 40-year old woman was first seen at the University of Minnesota Hospitals in September, 1949. Multiple nodules were present in both lungs at that time. The first of these was discovered on a routine chest film a year and one-half prior to admission.

Two nodules removed from the right lung in October, 1949, proved to be alveolar cell carcinoma. In December, 1949, a nodule in the left upper lung field was removed and this, likewise, was found to be an alveolar cell carcinoma. Bronchographic study shows the fine linear shadows of thread-like character representing the narrowed, compressed, rigid bronchi in the region of the tumor (Figure 3). It is notable that below the tumor area, in the more normal portions of the lung, the iodized oil does extend into the alveoli, to some degree.

Final admission to this hospital was in August, 1950, when the diagnosis of multiple brain metastases was made. The patient was discharged to her home.

Case 4: (Courtesy of Dr. M. B. Hanson, Abbott Hospital, Minneapolis, Minnesota). A 52-year old white female was admitted to Abbott Hospital in July, 1952. She had developed cough following "influenza" in October, 1951. In March, 1952, she was producing copious, yellow, watery sputum. There had been slight weight loss and dyspnea.

Examination of the chest revealed dullness over the left lower chest with amphoric breathing and coarse rales.

A roentgen examination in March, 1952, revealed a high degree of rather homogeneous density in the left lower lung field (Figure 4A). By the time of her

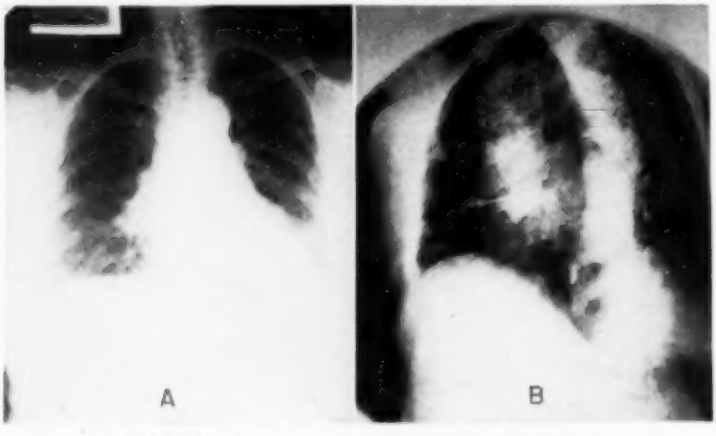

FIGURE 5A FIGURE 5B

Figure 5 (Case 5): *Alveolar cell carcinoma involving the right middle lobe alone. Figure 5A:* Postero-anterior roentgenogram demonstrating the area of density in the right middle lobe.—*Figure 5B:* Bronchogram shows again the rigid, somewhat narrow, poorly filled bronchi with little or no extension of the contrast medium into the smaller branches. Note the localized character of the bronchographic abnormality which involves only the middle lobe where the alveolar cell carcinoma was found.

admission the process had increased appreciably. The bronchogram revealed the findings shown in Figure 4B. The characteristic changes previously described are well shown here despite the extreme density of the lung which diminishes the contrast of the bronchographic material. The patient swallowed some of the iodized oil, hence the shadow of the esophagus and stomach is seen.

On October 10, 1952, thoracotomy was done with the removal of the greater portion of her left lung. The diagnosis of alveolar cell carcinoma was made from the sections.

Case 5: (Courtesy of Dr. Jack Friedman, Mt. Sinai Hospital, Minneapolis, Minnesota). A 72-year old white female was admitted to the Mt. Sinai Hospital on January 28, 1953, for a ligation of varicose veins of both legs. A slight cough had been present for years.

Routine admission chest film showed an enlarged right hilum shadow (Figure 5A). This was further investigated by bronchoscopy and bronchography. On the basis of the bronchographic appearance (Figure 5B) a diagnosis of alveolar cell carcinoma of the lung was suggested by one of us (N.Z.). Cytological studies and subsequent surgery verified the diagnosis unequivocally.

Case 6: A 53-year old white male was admitted to the University of Minnesota Hospitals on May 7, 1953, with a history of hemoptysis beginning approximately one year ago followed by progressive weight loss, cough, productive of a moderate amount of muco-purulent material, exertional dyspnea and left chest pain. Physical findings were those of pallor, general weakness and atelectasis of the left lower lung.

Roentgenograms of the chest revealed an extensive mass in the left lung with involvement of the pleura and evidences of atelectasis. A diagnosis of carcinoma of the left bronchus was made. A review of a photofluorogram, made two years before, then interpreted as negative, indicated that a nodule was already present in the periphery of the left lung at that time.

Bronchoscopy demonstrated displacement of the left lower lobe orifice but no visible neoplasm in the bronchus.

Bronchograms were then made and showed changes in the lower lobe bronchi similar to those described above. Even the bronchi of the second order exhibited narrowing, rigidity and complete filling but without any extension into the more peripheral bronchi. The findings were highly suggestive of alveolar cell carcinoma.

Left pneumonectomy was performed even though the tumor was known to involve the pleura and tracheo-bronchial lymph nodes, with the thought in mind of producing some palliation, but the patient expired on the seventh post-operative day.

Histological studies of the removed lung disclosed a typical alveolar cell carcinoma.

Comment

The six cases reported above show a characteristic similarity of their bronchographic appearance. The essential bronchographic findings have already been outlined.

It is noteworthy that since we have become aware of this bronchographic pattern we have been able to find seven cases of proved alveolar cell carcinoma, in which bronchographic studies were made. In these seven, six cases showed these typical deformities. In the one case which did not exhibit such bronchographic findings, there was an occlusion of the main bronchus to the involved area so that the smaller bronchi could not be demonstrated.

In the course of collection of these cases we found one (Case 1) with

the bronchial changes of the type herein described that bore the diagnosis of diffuse lymphangitic carcinoma of the lung. This was disturbing in that it presented the possibility of other lesions producing a similar roentgenographic finding. A recent review of the tissue sections by Dr. Robert Hebbel of the Department of Pathology, however, revealed that this, in actuality, was an alveolar cell carcinoma of the lung.

Reports by other authors in which bronchography was done in cases of alveolar cell carcinoma have universally indicated that the procedure was not of diagnostic aid. We can offer no plausible explanation for the discrepancy between their findings and ours.

A consideration of the gross and microscopic pathological alterations in this disease aids in the understanding of the bronchographic pattern. In contradistinction to primary bronchogenic carcinoma, there is no direct involvement of the bronchial mucosa; rather there is primary involvement of the alveoli and the bronchioles. These latter changes are reflected by loss of the normal "cushioning effect" of the peripheral ramifications which results in narrowing, elongation and rigidity of the bronchi. The appearance of the "leafless tree" and of the completely filled bronchi is explained by the failure of the opaque medium to gain ingress into the choked bronchioles and alveoli, compressed as they are by the ramifications of the tumor.

Although we have not yet encountered an exactly similar bronchographic picture in other lung lesions, the possibility that other types of pulmonary pathology will produce this is not, of course, excluded.

The appearance of the filled bronchus may be simulated by mucous plugging of the smaller bronchi such, for example, as is found in bronchial asthma. In these instances, however, the bronchi show a square or rounded, cut-off appearance and a normal or possibly even enlarged calibre, rather than the narrowing and tapering observed here.[11] Similarly, in normal cases the bronchi may present a filled appearance in the initial stage of the instillation prior to passage of the medium into the smaller branches. Many authors have called attention to the filling of the peripheral bronchi and of the alveoli in cases of other types of obstruction, such as that seen with bronchiectasis. Huizinga and Sypkens Smit[7] call particular attention to the complete filling of the large bronchi and the absence of extension into the peripheral bronchi and alveoli in cases of compressive atelectasis from a variety of causes. In such cases, however, the course of the bronchi is distorted, the caliber of the bronchi is greater than normal and the changes affect the bronchi of the second or third order. The appearance is strikingly different from that observed in this condition.

SUMMARY

1) A new diagnostic roentgen sign that is highly suggestive for a diagnosis of alveolar cell carcinoma has been described.

2) Bronchography in such cases presents a characteristic appearance. The bronchi are extremely narrow, uniformly distributed, rigid, filled

rather than coated, while the terminal bronchi and alveoli are free of contrast.

3) Six cases exhibiting this sign are presented.

RESUMEN

1) Se describe un nuevo signo radiológico que es altamente sugestivo de carcinoma de células alveolares.

2) La broncografía en tales casos, presenta una apariencia característica. Los bronquios son extremadamente estrechos, uniformemente distribuidos, rígidos, rellenos más bien que recubiertos, en tanto que los bronquios terminales y los alveolos no se llenan con el material de contraste.

3) Se presentan seis casos que muestran este signo.

RESUME

1) Les auteurs décrivent un nouveau signe radiologique hautement suggestif du cancer pulmonaire.

2) La bronchographie donne dans ces cas un aspect caractéristique. Les bronches sont extrêmement étroites, uniformément distribuées, rigides et emplies plutôt que simplement imprégnées par la substance de contraste qui n'atteint pas les bronches terminales et les alvéoles.

3) Les auteurs rapportent six cas illustrant ce signe.

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Acute Non-Aeration of Lung: Pulmonary Edema versus Atelectasis

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Probably no other diagnosis related to pulmonary disease has been abused as much as that of atelectasis. It is constantly being made where opacities are seen in roentgenograms of the chest in such situations as post-anesthetic states, barbiturate narcosis, chest wall injuries, prolonged rest in the supine position, poliomyelitis, bronchial asthma, pulmonary infections with retention of thick, tenacious mucus or exudate, and aspiration of foreign material or foreign bodies. Yet postmortem examination of the lungs from such conditions most often fails to reveal what is strictly defined as atelectasis. This discrepancy is probably due to misinterpretation of the actual alterations that usually transpire in the lungs in the aforementioned conditions. Atelectasis correctly defined refers to incomplete expansion of the pulmonary parenchyma at birth or to the collapse of varying portions of previously aerated lungs during later periods of life.[1] The usual mechanism which is thought to produce collapse of lung parenchyma is absorption of the alveolar air after the bronchus to a particular region has been obstructed. The other mechanism, compression of the lung, may be produced by alterations in the pleura, diaphragm, or chest wall. In the former mechanism, bronchial drainage is impaired, while in the latter it is not unless associated intrapulmonary disease is present. In microscopic sections, the walls of the alveoli, alveolar ducts, and respiratory bronchioles are closely opposed to form slit-like spaces with the walls often paralleling each other. The alveolar capillaries appear to be dilated, but it has been shown that less blood flows through an atelectatic lung than a normal expanded one. This report is concerned with experimental and clinical observations relative to the previously stated discrepancy between clinical and post-mortem findings.

Experimental Procedure and Observations:

Twelve healthy, mongrel dogs of approximately the same weight and age and kept under the same conditions were put under light sodium nembutal narcosis. Through a bronchoscope, the major bronchus to a left lower lobe in each dog was obstructed with a plug of absorbent cotton (Tampax) saturated with 1 per cent procaine hydrochloride. This was pushed down into the bronchus so that it would fit snugly. The dogs were then allowed to come out of the narcosis and were all alert within one hour of the procedure. Three dogs were sacrificed at 6, 12, 24, and 36 hour intervals following obstruction to the bronchi. The dogs were killed within

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the period of a few minutes by use of a carbon monoxide chamber. Immediately following sacrifice, the dogs were autopsied. The trachea was tied off in the neck before entering the chest and the lungs, trachea and heart were then removed in toto. The bronchus with the plug of cotton in situ was identified in all instances. After gross examination, numerous sections were taken from the position of lung distal to the obstructed bronchus, as well as from the non-obstructed lobes on the same and opposite sides. These sections were stained with hematoxylin and eosin and Masson's trichrome stain.

In the three animals sacrificed at six hours, no significant gross changes were found in the areas of lung obstructed as compared to the contralateral lungs and non-obstructed lobes on the same side. Microscopic examination revealed the only alteration to consist of congestion of the alveolar capillaries of the obstructed lobe. There was no reduction in size of the obstructed lobe. The alveoli still appeared to be normally distended. The other lobes were not congested (Figure 1).

Three animals sacrificed at 12 hours revealed essentially the same findings as the six hour animals with the exception that the congestion was more pronounced and in some of the alveoli there were accumulations of transudate. This was not present in the other areas of lung tissue.

In the 24 hour animals, there were slight reductions in the size of the lobes of lung distal to the obstructions. Practically all of the alveoli in the obstructed regions were filled with fluid. The alveolar walls were not collapsed against each other and the reduction in the size of the alveoli was slight (Figure 2). The other areas of the lungs did not reveal any significant congestion or edema.

In the 36 hour animals, the lungs distal to the obstructions were distinctly reduced in size, but not completely so, and on histologic section revealed alveoli reduced in size, marked congestion of the alveolar capillaries, and intra-alveolar fluid containing numerous polymorphonuclear leucocytes (Figure 3). The unobstructed lobes did not reveal anything unusual.

Thus the progression of events beginning with the six hour period: At first congestion of the alveolar capillaries; a few hours later pulmonary edema developed; subsequent to this there was reduction in distention of lung tissue which contained fluid with numerous polymorphonuclear leucocytes.

Post-mortem Observations On Human Lungs:

There were 20 cases of barbiturate poisoning, 30 of brain injuries with deaths occurring immediately following the injury to several days later, 20 fatal cases of poliomyelitis, 10 with chest injuries of varying types and degree, 4 deaths from bronchial asthma, a few cases of various types of bronchial obstruction, and several anesthetic and post-anesthetic deaths. All of these were examined carefully to determine the degree of pulmonary edema, congestion, atelectasis, and pneumonia that might be present. In all of the barbiturate cases, regardless of the time interval from the

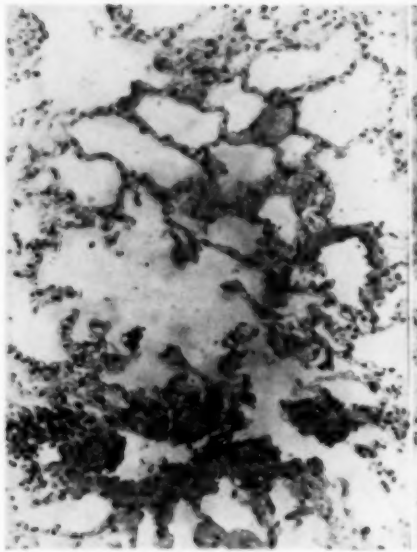

FIGURE 1

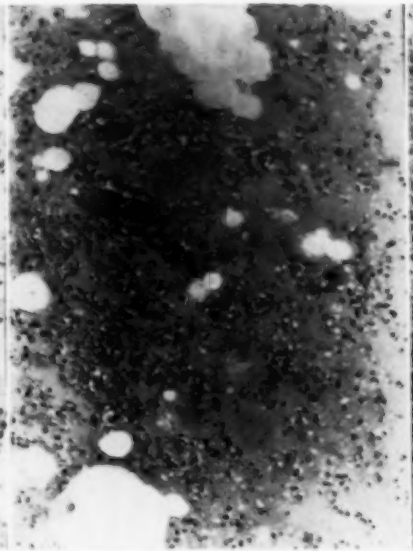

FIGURE 2

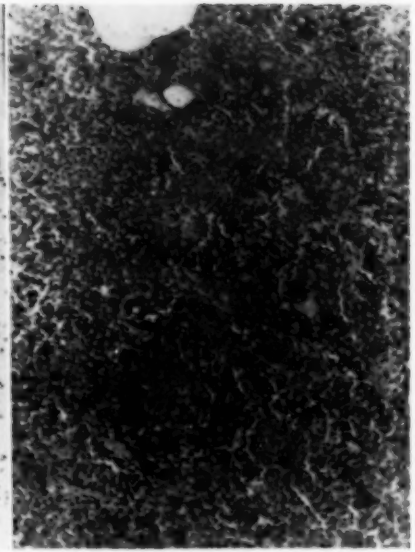

FIGURE 3

Figure 1: Photomicrograph (H & E—250 x) of lung in dog sacrificed six hours after obstruction to bronchus. This shows alveolar capillary congestion.—*Figure 2:* Photomicrograph (H & E—250 x) of lung in dog sacrificed 24 hours after bronchial obstruction. This shows edema and congestion.—*Figure 3:* Photomicrograph (H & E—250 x) of lung in dog sacrificed 36 hours after bronchial obstruction. This shows some alveolar collapse, edema, and extensive infiltration with leucocytes.

ingestion of the barbiturates to the time of death, areas of colalpsed lung were not found. Considerable congestion and varying degrees of focal and diffuse edema, and occasionally lobular pneumonia were present (Figure 4). In the traumatic cerebral cases, even when death was almost instantaneous, the congestion and edema of the lungs was diffuse and extensive. Atelectasis was not found in the cases surviving several days, despite the accumulation of thick and tenacious exudate in many of the bronchi and bronchioles. Areas of lung distal to these bronchi were markedly edematous and congested and in numerous instances revealed pneumonia. In the poliomyelitis cases, a somewhat different picture was present. In all of them, therapeutic drainage of the bronchial tree was maintained through suction, bronchoscopy, or a tracheotomy tube. The lungs varied in appearance. In some, there were areas of congestion and edema. In the posterior lower aspects of the lungs, areas of edema were often intermingled with small focal areas of atelectasis in which the alveolar walls were actually in contact with each other (Figure 5). This occurred regardless of the presence or absence of exudate in the bronchioles. In the chest injuries, the usual findings consisted of varying degrees of hemorrhage in the alveoli beneath the pleura immediately adjacent to the site of the injury with areas of edema adjacent to this (Figure 6). Pulmonary edema was also present remote from the site of injury. Atelectasis was not found. Two cases of bronchial obstruction were of particular interest. The first, a robust, adult Negro male with a compression injury of the chest was given oxygen by means of a mask. While receiving oxygen, his condition

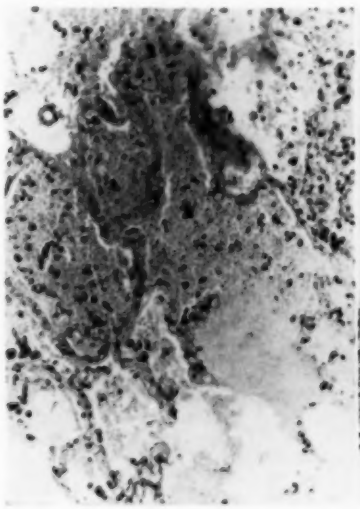

FIGURE 4

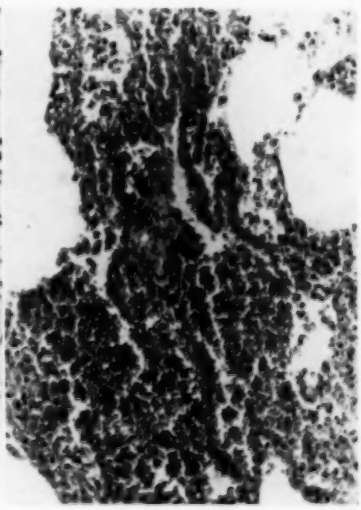

FIGURE 5

Figure 4: Photomicrograph (H & E—250 x) of lung in case of barbiturate narcosis. This shows congestion and edema.—*Figure 5:* Photomicrograph (H & E—250 x) of lung in case of poliomyelitis. This shows focal atelectasis.

rapidly grew worse and he expired after receiving oxygen for eight hours. At postmortem examination, it was found that the plastic disc in the oxygen mask had slipped off the valve and had become lodged in the carina completely obstructing the main bronchus to the right lung. In this lung, there was marked congestion and edema, but reduction in the size of the lobe was scant. In the other case, the obstruction was of a more chronic nature. This case was one of bronchial asthma in which the mucoid exudate in a bronchus to an upper lobe segment had become inspissated and obstruction developed over a period of time. Behind this obstruction to the bronchus, which was ulcerated at the region of the mucoid impaction, there was edema, mononuclear cell infiltration, and beginning organization of the exudate. There was no atelectasis. The constant findings in these groups of cases were varying degrees of congestion, edema, occasional small focal areas of atelectasis, and pneumonia. The focal atelectasis was limited almost entirely to the cases of poliomyelitis.

Discussion:

The findings of congestion, edema, and some reduction in the size of lung with an infiltration of inflammatory cells in the dogs with obstructed bronchi would indicate that in many instances shadows appearing in the chest roentgenograms are at first primarily caused by congestion and edema. The reduction in the size of the lungs and the inflammatory

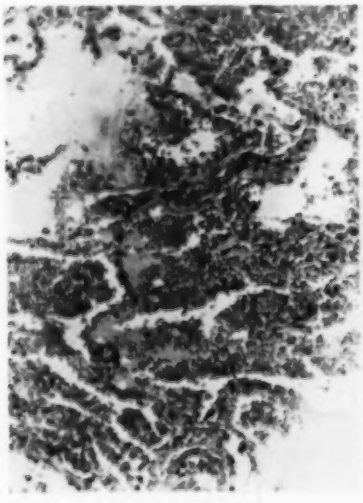

FIGURE 6

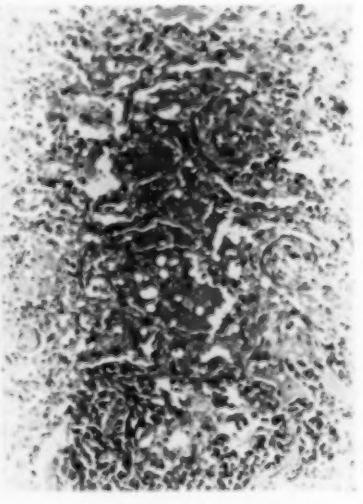

FIGURE 7

Figure 6: Photomicrograph (H & E—250 x) of lung in case of blunt trauma to chest cage. This shows edema and intra-alveolar hemorrhage. — *Figure 7:* Photomicrograph (H & E—250 x) of lung in case of mucoid impaction of the bronchus in bronchial asthma. This shows edema, leucocytic infiltration, and some fibrosis.

exudate appear somewhat later. Within 36 hours it was necessary to consider the process as pneumonia. Drinker[2] in his experimental observations states that the development of the edema is due to anoxia. The alveolar capillaries depend for their oxygen supply upon the alveolar air. If this is shut off or reduced, the alveolar capillaries are deprived of the oxygen and the capillary endothelium becomes more permeable. This permits fluid and cells to accumulate in the alveolar spaces. Another explanation offered for the development of edema following bronchial obstruction is a mechanical one. It is claimed with absorption of air distal to the obstruction a negative pressure is exerted on the alveolar capillaries with the resultant sucking of fluid from the capillaries into the alveolar spaces.[3] It would seem from most experimental and clinical evidence that the former explanation is the most important and valid one. In some other experimental studies, obstruction of the larger bronchi has produced real atelectasis without edema.[4] However, in these studies, the bronchi were obstructed through an open chest and after the lung was collapsed from the pneumothorax created by the procedure. This would explain the differences in the findings of this study as compared to that of others.

Analysis of the postmortem findings in the human lungs is consistent with that observed in the dogs. In addition to the experimental procedure described in this report, others have produced pulmonary edema in dogs with acute peripheral blood loss, with blunt injuries to the chest wall, with the maintainance of dogs in a state of narcosis and in the supine position.[5-8] Increased intracranial pressure in dogs also results in pulmonary edema. In all of these animals, the predominant findings were congestion and edema and only insignificant degrees of atelectasis. The case of bronchial asthma with a bronchus obstructed by laminated inspissated mucoid exudate is similar to other cases reported by Shaw.[9] In this situation, the findings undoubtedly represent the earlier stage of what McDonald et al.[10] have described as obstructive pneumonitis of neoplastic origin. These authors point out the error of referring to these changes as atelectasis. In an extensive personal experience with neoplastic obstruction of the bronchi, the experience is similar to that reported by McDonald. In most of the aforementioned clinical conditions there are multiple factors present which facilitate the development of the described changes. For instance, in cases of trauma to the brain there are neurogenic and neuromuscular factors involved in the production of pulmonary edema, as well as interference with pharyngeal, laryngeal, and cough reflexes. Thus a combination of events which produce edema and interference with the removal of this accumulated fluid is present. Patients in these various categories are usually in the supine position so there would be the development of congestion and edema in the dependent portions of the lungs. The same multiple factors are present in barbiturate narcosis, post-anesthetic conditions and poliomyelitis.

The occasional cases of acute massive collapse of the lung which occur usually in anesthetic and post-anesthetic states do not fit into the above categories. In this situation the lungs become collapsed within a matter

of a few minutes and real atelectasis without significant edema is present. Among the cases studied, there was one which belonged in this group. This was a young female who was given nitrous oxide anesthesia during the final stages of labor. After the anesthesia was given for a period of 20 minutes, it was noted that the patient was dead. Postmortem examination revealed massive collapse of both lungs with numerous loose mucus plugs diffusely distributed throughout the bronchial tree. Microscopically, atelectasis was present. The alveolar and bronchiolar walls were collapsed against each other. There was no edema. There have been numerous attempts to explain this development on a rational basis. None has been completely satisfactory. A logical and ingenious explanation has recently been offered by Viswanathan.[11] He contends that the mucus secretions in the bronchioles instead of producing complete obstruction act like ball-valves allowing air to get out from the lungs during expiration and preventing air from entering during inspiration. This may cause collapse of the lung within a few minutes even before edema can develop. The ball-valve action is possible because the bronchi are not of the same caliber throughout their length. The mechanism is accelerated by the tendency of the lung to shrink owing to its elasticity. Absorption of air behind a completely blocked bronchus obviously cannot explain the sudden collapse since this would take at least several hours. In all of these conditions, one of the most important defense mechanisms necessary to maintain adequate aeration of the lungs, that is, collateral ventilation, is interfered with. Maintenance of adequate collateral ventilation is dependent upon a propor functioning neuromuscular apparatus, as well as patency of the smaller bronchioles.[12] In both the experimental studies and in the human cases, congestion and edema developed very early from multiple causation. Any subsequent reduction in the size of the lung would then be superimposed on this pre-existing edema and congestion. The sum total of the final picture, depending on the duration and circumstances involved, is a combination of congestion, edema fluid, inflammatory cell infiltration, and varying degrees of reduction in size of the lungs due to the absorption of air. Without antibiotic therapy, this is the ideal background for the development of pneumonia. Simple collapse of the lungs, as in compression atelectasis following artificial pneumothorax in which none of the above factors are operating and in particular in which the bronchial drainage is not impaired does not predispose towards infection. It is important to note that despite the terminology one wishes to choose, whether this be atelectasis, wet atelectasis, collapse of the lung, edema, or atelectatic pneumonia, what the mechanism and pathogenesis of the lesion is and what the ultimate consequences might be. The use of the term acute non-aeration of lung is suggested to describe these x-ray picture shadows because it is non-specific and yet recognizes the fundamental functional alteration that is present. In any individual situation of this sort it is difficult to be certain of the proportions of congestion, edema, pneumonia, and actual collapse present on clinical and roentgenographic grounds.

SUMMARY

1) Sudden complete obstruction of major bronchi in dogs with intact chests resulted in a series of events over a 36 hour period. Pulmonary congestion, edema, partial collapse, and infiltration with leucocytes (pneumonia) developed in the sequence listed.

2) Post-mortem observations on the lungs from such conditions as bronchial obstruction, barbiturate narcosis, chest injuries, poliomyelitis, and post-anesthetic states revealed congestion, edema, and pneumonia. The degree of lung collapse, if present, was usually variable and insignificant.

3) The term acute non-aeration of the lung is suggested to replace the term atelectasis in those situations where it is used erroneously.

RESUMEN

1) Como consecuencia de la obstrucción repentina de los bronquios principales de perros con tórax intacto, ocurrieron algunos cambios dentro de un periodo de 36 horas. Se presentaron: congestión pulmonar, edema, colapso parcial e infiltración con leucocitos (neumonía) en el orden citado.

2) Los exámenes de pulmones a la autopsia cuando los sujetos habían presentado afecciones tales como obstrucción bronquial, narcosis con barbitúricos, lesiones del tórax, poliomielitis, y estados postanestésicos, demostraron la presencia de congestión, edema, y neumonía. El grado del colapso pulmonar si existía, era habitualmente variable e insignificante.

3) Se sugiere el término "no aereación aguda del pulmón," para substituir el de atelectasia en esas situaciones, en las que ha sido erróneamente aplicado.

RESUME

1) Une obstruction soudaine et complète de la bronche souche chez le chien, sans lésion pulmonaire, survint dans une période de 36 heures à la suite de manifestations variées. On constata congestion pulmonaire, oedème, collapsus partiel, et infiltration leucocytaire (pneumonie).

2) L'examen post-mortem des poumons atteints d'obstruction bronchique, d'anesthèsie barbiturique, de traumatismes thoraciques, de poliomyélite et dans la phase post-anesthésique, mit en évidence congestion, oedème et pneumonie. L'importance du collapsus pulmonaire, si toutefois il existe, était généralement variable et insignifiant.

3) L'auteur propose que l'expression d'atélectasie soit remplacée dans les cas où elle est utilisée d'une façon erronée, par celle de "inaération aigue du poumon".

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Isoniazid in Pulmonary Tuberculosis*

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This study was undertaken early in 1952 for the evaluation of results and complications in the treatment of pulmonary tuberculosis with isonicotinic acid hydrazide (isoniazid). Sixty two patients were observed for a period of from 90 to 297 days with an average of 151 days.

CONDITION OF THE PATIENTS AT THE BEGINNING OF THE STUDY

EXTENSION

Minimal	6
Moderately Advanced	23
Far Advanced	33

DISTRIBUTION

Unilateral	17
Bilateral	45

TYPE

Exudative	21
Mixed	33
Productive	8

Sexual Distribution: Males 35; Females 27.
The age ranging between two and 90 years. Average age: 35 years.

At the start of this observation, 52 patients had positive while 10 had negative sputa. They presented the clinical symptomatology classical for the disease in accordance with the form and extension. The symptomatology will be analyzed in detail with the evaluation of results.

Endobronchial tuberculosis demonstrated by direct examinations of the larynx and tracheobronchial tree were found in 34 of the patients. One had a tuberculous ulcer of the base of the tongue (proved by biopsy) and another, tuberculous peritonitis; while another had pleurisy with effusion.

Dihydrostreptomycin and para-aminosalicylic acid had been administered previously to 48 while 14 had not received any antibiotics. The total amount ranged between 7 and 112 gms. of dihydrostreptomycin administered in doses of 1 gm. intramuscularly, twice a week, and between 210 and 2,280 gms. of PAS in three equal portions of 4 gms. daily with meals.

Sputum cultures revealed organisms with absolute resistance to dihydrostreptomycin and PAS in 20 cases; six with resistance to dihydrostrepto-

*From the Chest Service, Gorgas Hospital, Ancon, Canal Zone.
Presented at the 554th meeting of the Medical Association of the Isthmian Canal Zone, January 20, 1953.
The drug used in this investigation was donated by the following laboratories: E. R. Squibb and Sons (Nydrazid); Eli Lilly and Co. (I.N.H.) and Chas Pfizer and Co. (Cotinazin). Although they are marketed under different names, these products have exactly the same structure.

mycin alone and five to PAS. These patients have been included because it has been proved that isoniazid has the same effect on organisms resistant to other drugs as on those that are sensitive.

Before the administration of the drug, pneumoperitoneum had been established in 32 cases. One had spontaneous pneumothorax. Five cases had been submitted two years previously to total thoracoplasty. One to first stage thoracoplasty and two had phrenic crush. Two had allergic rhinitis; four had intestinal ankylostomiasis. Pregnancy (three and four months) was found present in two patients when the drug was started, both having delivered normal children entirely free of any toxic manifestation.

The period of observation, prior to the start of this study extended in 47 cases from three to 60 months with an average of 20 months. During this time they did not show any significant clinical, roentgenological, or laboratory changes; the process maintaining itself in an absolute stationary status. Two showed progression of the lesions. The other 15 received the drug at the time of diagnosis.

During this investigation 13 patients were started on pneumoperitoneum and one on pneumothorax. One had first stage thoracoplasty, two had lobectomies, three segmental resections, one wedge resection and one pneumonectomy.

Results should be accepted on the understanding that in the course of an investigation patients cannot be denied additional forms of therapy considered beneficial.

Methods of Investigation

All the patients were submitted to clinical examination and laboratory study prior to the administration of isoniazid. Consultations were asked from other services whenever considered necessary.

The following basic examinations were routinely done:

1) Roentgenographic study of the thorax.
2) Laryngoscopy and bronchoscopy.
3) Electrocardiogram.
4) Chemical examination of the blood:
   - Fasting blood sugar
   - Cholesterol
   - NPN
   - Chlorides in the form of NaCl
   - CO_2 combining power
   - Total proteins
   - A/G Ratio
   - Icteric Index
   - Quantitative bilirubin
   - Cholesterol chephalin flocculation test.
5) Cellular examination of the blood:
   - Total erithrocytic count
   - Leucocytes and differential count

Thrombocytes
Sedimentation rate
Bleeding and Clotting time.

6) Routine urinalysis.

These examinations were repeated monthly for evaluation with exception of the EKG that was done every three months and bronchoscopy every six weeks in cases with endobronchial disease.

The regular diet provided them an average of 3,500 calories daily, with 60 gms. of proteins and was supplemented with multivitamins.

All were hospitalized during the course of this investigation.

Dosage and Regimen

The great majority of studies reported to date have been based on dosages of isoniazid which ranged between 2 to 5 mgm. per kilo of body weight, demonstrating these dosages to be well tolerated. This study was started using 4 mgm. per kilo of body weight of isoniazid, given orally in two doses after breakfast and dinner. Later this dosage was increased to 8 mgm. per kilo of body weight in some patients, while others were given 8 mgm. from the start. A last group received combined therapy of the isoniazid and dihydrostreptomycin, 1 gm. intramuscularly twice a week.

Results

Tuberculosis is both a local and generalized disease. Toxic manifestations such as asthenia, elevation of temperature, loss of weight, anorexia, and others constitute the general symptomatology.

The local bronchopulmonary and ulcerative lesions are determined by radiological shadows, bacteriological examinations and bronchoscopy.

Changes in the General Manifestations

On initiation of the drug, the toxic manifestations of the disease disappeared rapidly with a notable improvement in the attitude and general condition of the patient.

Temperature: Sixteen patients had fever at the beginning of therapy, with elevations as high as 104 degrees F., some of which had been maintained up to four months. All temperatures became normal within the first 10 days of treatment, some with a more or less precipitous fall within five days, remaining normal thereafter. This impressive fall in temperature occurs regardless of the length of time the febrile state had been present, or the type and extension of the disease. It is observed regardless of age, race or sex. It is noticed just as fast in patients on 4 mgm. per kilo of body weight as in those receiving 8 mgm. per kilo so that the difference in dosage does not seem to be important. It is also noticed in patients under combined drug therapy.

Appetite and Weight: The patients receiving isoniazid have been described to have a voracious appetite. Special diets were not administered. Patients were given all they desired and could eat. The diet on our service furnishes an average of 3,500 calories daily, but with the amount of food

ingested by these patients, the number of calories must have multiplied enormously.

The anorexia that is found with routine monotony in the tuberculous patient disappeares promptly; this coinciding in time with the loss of toxicity and the fall in temperature to normal.

The increase in appetite is not due to a local stimulation of the drug as this is administered after meals; on the other hand, at breakfast, when the concentration of the drug is at its lowest level, the patients eat just as much as in other meals.

This unsatisfiable appetite appears just as well and as soon in those receiving 4 mgm. per kilo of body weight as in the others. There is no further increase in appetite with higher dosages.

Maybe the most spectacular part in the treatment with isoniazid is the rapid weight gain. This becomes apparent after the second or third week, and is more accentuated in those that are far below their normal weight at the start of medication. There is a tendency to stabilization once normal weight or a little more is reached.

Of the 62 patients presented, 53 were between five and 55 lbs. with an average of 24 lbs. below their normal weight, taking into consideration sex, height, age, and body frame.

A weight gain between three and 35 lbs. with an average of 18 lbs. occurred in 54 patients. Of the eight who did not show any weight gain, five were within or above normal weight at the start of the drug; two were mental cases and one simply did not show any gain.

Gain in weight cannot be accepted as an exact indication of the condition nor the state of the lesions; however, the rapidity of inversion of the weight gain curve as soon as the normal metabolic mechanism is restituted and the toxicity of the process is eliminated, is remarkable.

It is considered that the increase in weight is due to the abnormal appetite that these patients develop which makes them ingest fabulous quantities of food. It is not explainable on the basis of fluid retention in the body. None of the patients showed any clinical evidence of edema, ascites or anascarca.

Changes in the Local Lesions

Cough and Expectoration: Improvement in cough begins during the first week of treatment. Those who had shown resistance to other types of medications improved in a few days.

Cough and expectoration disappeared completely in all patients with the exception of one with tuberculous laryngitis in whom the organisms became resistant to isoniazid; the cough continued but changed to dry and non-productive.

The character of the sputum tends to change, becoming thinner before its total disappearance. The complete disappearance of sputum in the presence of radiographic evidence of ulcerations is of marked clinical significance.

Bacteriological examinations of sputum and gastric washings: Bacterio-

logical examination of the sputum is done monthly on three consecutive days. This includes direct smear, concentrations and cultures. Whenever the direct smear and concentrations are reported as negative, we proceed to do monthly examination of gastric material also on three consecutive days and including direct smear, concentrations and cultures.

Positive cultures are investigated for possible resistance of the Mycobacterium tuberculosis to streptomycin, para-aminosalicylic acid and since the start of this study, to isoniazid.

Based on previous experiences with dihydrostreptomycin and PAS in which resistant strains of Mycobacterium tuberculosis to these drugs were found in patients who had never received them, it was decided to do an initial study of resistance to isoniazid before administering the drug to patients with positive sputum. Of 97 sputa and gastrics that were examined, nine were proved in repeated examinations, to be resistant to isoniazid in a concentration of 10 mcg. per mililiter. This "initial," "natural," or "spontaneous" resistance has been previously reported and should be kept in mind in cases of therapeutic failures in which resistance tests have not been initially done.

No quantitative studies of bacilli were attempted. The study was limited to observe the presence or absence of the organisms.

Fifty two cases were found to be positive while 10 were negative at the start of the observations. Conversion of the sputa to negative according to extension and type of lesions is shown in Tables I through VIII.

Of the 32 patients who received isoniazid alone, 16 reverted to negative (50 per cent).

This reversion occurred in every case within 30 to 60 days of treatment. Of the 21 who received combined streptomycin-isoniazid, 10 (47.6 per cent) reverted to negative *within 30 days*. Four with far advanced disease were

PATIENTS ON 4 MGM. PER KILO OF BODY WEIGHT:

TABLE I

	Total	Negative	Per cent
Moderately Advanced	6	6	100
Minimal	1	1	—
Far Advanced	6	2	33.3
TOTAL	13	9	69

TABLE II

	Total	Negative	Per cent
Exudative	7	6	85.7
Mixed	5	3	60
Productive	1	—	—
TOTAL	13	9	69

PATIENTS ON 8 MGM. PER KILO OF BODY WEIGHT:

TABLE III

	Total	Negative	Per cent
Minimal	—	—	—
Moderately Advanced	4	3	75
Far Advanced	15	4	26.6
TOTAL	19	7	36.7

TABLE IV

	Total	Negative	Per cent
Exudative	2	—	—
Mixed	12	6	50
Productive	5	1	20
TOTAL	19	7	36.7

TOTAL OF PATIENTS ON ISONIAZID:

TABLE V

	Total	Negative	Per cent
Minimal	1	1	—
Moderately Advanced	10	9	90
Far Advanced	21	6	28.5
TOTAL	32	16	50

TABLE VI

	Total	Negative	Per cent
Exudative	9	6	66.6
Mixed	17	9	53
Productive	6	1	16.6
TOTAL	32	16	50

PATIENTS RECEIVING DIHYDROSTREPTOMYCIN AND ISONIAZID:

TABLE VII

	Total	Negative	Per cent
Minimal	1	1	—
Moderately Advanced	7	5	71.4
Far Advanced	13	4	20.7
TOTAL	21	10	47.5

TABLE VIII

	Total	Negative	Per cent
Exudative	8	5	62.5
Mixed	11	5	45.4
Productive	2	0	—
TOTAL	21	10	47.6

Of the 32 patients who received isoniazid alone, 16 reverted to negative (50 per cent).

still positive after the dosage had been increased from 4 mgm. to 8 mgm. per kilo of body weight. Of 10 moderately advanced cases who received the drug, nine (90 per cent) reverted. Of 21 far advanced cases, six (28.5 per cent) reverted to negative. On consideration of the type of lesion the rate of regression was as follows: six negative out of nine exudative cases. Nine negative out of 17 mixed cases and only one negative out of six productive cases.

The highest rate of reversion is obtained in early exudative cases. Of a total of 21 positive cases who received combined treatment, 10 (47.6 per cent) reverted to negative. All reversions occurred within 30 days.

Cases that had previously received dihydrostreptomycin and PAS reverted to negative when given isoniazid: five cases out of 20 who were originally resistant to streptomycin and PAS as well as two out of five resistant to PAS also reverted. All cases included in this group were far advanced with the exception of one moderately advanced.

All cases who became negative have remained so.

Six cases with initial resistance to isoniazid were submitted to treatment to demonstrate possible differences in vivo and in vitro. All continued to be resistant although they have shown systemic benefits from the drug, such as detoxication, increase in weight averaging 15 to 21 pounds, drop in temperature to normal, and loss of cough and expectoration, making pneumonectomy possible in one case, thanks to the general improvement of the patient.

Of the 52 cases who were positive 12 (21.8 per cent) developed resistance to isoniazid in the course of investigation. Three of these became resistant within 30 days when the dose of isoniazid was increased from 4 mgm. to 8 mgm. per kilo of body weight.

Five of the resistant cases were on combined therapy, and of these, four developed an absolute resistance to streptomycin after 30 to 90 days.

It is noteworthy that these four patients had been previously on dihydrostreptomycin and that resistance to both drugs appeared after the addition of isoniazid. This finding does not seem to concur with recent reports to the effect that the use of both drugs seems to lengthen the time necessary for the organisms to develop resistance.

Roentgenographic Changes

X-ray film changes have been described as the least impressive results of the treatment with isoniazid, differing so from streptomycin administration in which early and significant changes in the x-ray film shadows are obtained.

Tables IX through XIV will show the results obtained in this study.

Twelve whose dose was increased from 4 to 8 mgm. per kilo of body weight did not seem to benefit by the new dosage.

On four the dosage was reduced from 8 mgm. to 4 mgm. per kilo, not

PATIENTS RECEIVING 4 MGM. PER KILO OF BODY WEIGHT:

TABLE IX

	Total	Improved	No Change	Worse	Days	Per cent
Minimal	2	2	-	-	64-65	—
Moderately Adv.	9	9	-	-	64-114	100
Far Advanced	9	4	4	1	61-161	44.4
TOTAL	20	15	4	1		75

TABLE X

	Total	Improved	No Change	Worse	Days	Per cent
Exudative	10	8	1	1		80
Mixed	9	7	2	0		77.7
Productive	1	0	1	0		—
TOTAL	20	15	4	1		75

PATIENTS THAT RECEIVED 8 MGM. PER KILO OF BODY WEIGHT:

TABLE XI

	Total	Improved	No Change	Worse	Days	Per cent
Minimal	3	3	-	-	50-114	100
Moderately Adv.	13	12	1	0	40-166	92.3
Far Advanced	19	6	10	3	21-182	31.5
TOTAL	35	21	11	3		60

TABLE XII

	Total	Improved	No Change	Worse	Days	Per cent
Exudative	11	9	1	1		81.8
Mixed	18	11	5	2		61.1
Productive	6	1	5	-		16.6
TOTAL	35	21	11	3		60

TOTAL PATIENTS RECEIVING ISONIAZID:

TABLE XIII

	Total	Improved	No Change	Worse	Days	Per cent
Minimal	5	5	-	-	50-114	100
Moderately Adv.	22	21	1	-	40-166	95.4
Far Advanced	28	10	14	4	21-182	35.7
TOTAL	55	36	15	4		65.2

TABLE XIV

	Total	Improved	No Change	Worse	Days	Per cent
Exudative	21	17	2	2		81
Mixed	27	18	7	2		61.6
Productive	7	1	6	-		14.2
TOTAL	55	36	15	4		65.2

showing any progression of disease or reappearance of symptoms.

All minimal cases improved. Twenty one (95.4 per cent) of 22 moderately advanced cases showed regression of disease while only 10 (35.7 per cent) of 28 far advanced cases demonstrated improvement by x-ray film. According to the type of lesions, the results obtained were: 17 of 21 exudative type improved, 18 of 27 mixed type and one of eight productive type improved.

It has been observed that in the mixed type of disease only the exudative element seem to clear up on x-ray films (Tables XV and XVI).

PATIENTS RECEIVING DIHYDROSTREPTOMYCIN AND ISONIAZID:

TABLE XV

	Total	Improved	No Change	Worse	Days	Per cent
Minimal	1	1	-	-	147	—
Moderately Adv.	12	9	3	-	85-188	75
Far Advanced	13	6	5	2	90-203	46.1
TOTAL	26	16	8	2		61.5

TABLE XVI

	Total	Improved	No Change	Worse	Days	Per cent
Exudative	11	9	1	1		81.8
Mixed	13	6	7	-		46.1
Productive	2	1	0	1		50
TOTAL	26	16	8	2		61.5

Twenty six received combined dihydrostreptomycin and isoniazid therapy. Sixteen presented improvement of the lesions on roentgenograms. The one minimal case, nine (75 per cent) of 12 moderately advanced and six (46.1 per cent) of 13 far advanced.

Type differentiation showed improvement in nine (81.8 per cent) of 11 exudative cases; six (46.1 per cent) of 13 mixed type; and only one of two productive cases.

Bronchoscopy

Two with active tuberculous laryngitis improved. Two with ulcerative endotracheal lesions showed marked regression, they are still on treatment.

All of 23 with endobronchial lesions ranging from simple hyperemia of secondary orifices to frank granulations and stenosis of the main stem bronchus improved. Two have marked residual stenosis.

Laboratory Examinations

Urine: Urinary observations are of particular importance as this constitutes the principal route of elimination of the drug. Albumen and occasional casts have been reported by other observers. We have not been able to confirm their finding.

Blood: No deviation from the normal has been found in the total white count. Five showed eosinophilia ranging from 5 to 15 per cent. The patients presented slight tendency to an increase of 1.5 to 2 gms. of hemoglobin with slight elevation in the erithrocitic count. The reverse, that is, a slight decrease have been reported in other studies.

No changes in the platelet count and bleeding or clotting time have been found. Some authors, especially the Europeans insist that there is a marked tendency to hemoptysis in patients receiving isoniazid and they seem to find it in a large percentage of cases. We have not confirmed this bleeding tendency, but should it exist, it probably would not be due primarily to the already mentioned changes in the blood but rather appears as a phenomenon which accompanies the re-epithelization of the cavities that occurs with the administration of the drug.

Sedimentation Rate: Regardless of the clinical improvement there was an elevation of the sedimentation rate ranging between 6 and 16 mm. in nine cases.

Blood Chemistry:

1) FBS: no variation
2) NPN: no change
3) Blood chlorides in form of sodium chloride: there was no deviation from normal
4) Cholesterol: no change
5) Icteric index: no patient showed any abnormality
6) Quantitative bilirubin: no alteration
7) Total protein and albumen-globulin ratio: there were no changes in the total proteins of the blood serum, they remained within normal range, but within this normal range there is a tendency, as evidenced in 14 cases,

to an increase in the globulin fraction with a decrease in the albumen fraction. The increase in globulin over normal values ranged between 0.5 and 1.5 gms. in 100 cc. resulting in an inversion of the albumen-globulin ratio. Other liver function tests on these cases did not show any evidence of hepato-celular damage nor were there any clinical sings of hepatic disease.

No satisfactory explanation to this phenomenon can be given at this time. It probably does not represent any permanent liver damage as the cephalin-flocculation test of Hanger remains normal in all cases; possibly it may represent a reversible process that disappears on discontinuing the drug as do other hepatic alterations reported by other authors but not found by us.

Electrocardiogram: studies remained normal throughout the investigation. Before receiving the drug, a patient showed inversion of T waves and depression of ST segment with a tendency to right heart strain; these findings did not vary during the study.

Toxicity: caused by the drug was not marked and considered of not much clinical importance. The only toxic manifestations found in 4 mgm. per kilo of body weight consisted of insomnia in one patient after 35 days; nausea in another after 63 days; and a generalized pruritus after 53 days without visible skin lesions and which responded to pyribenzamine.

When the dosage was increased to 8 mgm. per kilo of body weight, the following toxic reactions appeared:

1) Insomnia in 14 cases, 13 moderate and one more troublesome, reported between 10 and 110 days. All responded quickly to barbiturates.

2) Nervousness: hyperirritability in two cases occurring six to 10 days after receiving the drug and also responding to the barbiturates without being necessary to discontinue the drug.

3) Seven had nausea accompanied by headache and dizziness, four weeks after receiving the drug. The medication was discontinued for a few days and the toxic symptoms subsided. The drug was re-started with dosages of 4 mgm. per kilo without reappearance of toxic symptoms.

4) Vomiting occurred in four cases after 70 days of treatment, disappearing when the drug was discontinued.

5) Paresthesia was experienced in one patient after 60 days. Constipation and difficulty in urination have been reported by others but not observed by us on the dosages used.

SUMMARY AND CONCLUSIONS

Sixty two cases of active pulmonary tuberculosis treated with isonicotinic acid hydrazide over a period of from 90 to 297 days have been reported. The drug was administered in dosages of 4 mgm. and 8 mgm. per kilo of body weight.

Twenty six received combined treatment of dihydrostreptomycin and isoniazid. In spite of the small number of cases it is considered that some of the results are significant.

General manifestations of pulmonary tuberculosis disappeared in two to

three weeks, temperature becoming normal, with considerable weight gain and development of voracious appetite.

Cough and expectoration were completely eliminated.

Of 32 positive cases that received isoniazid, 16 reverted to negative.

Of 21 positive cases that received combined dihydrostreptomycin and isoniazid 10 reverted. The reversions were higher in the early exudative and mixed cases.

All laryngeal and endobronchial lesions responded favorably.

Roentgenological changes were not as impressive as the clinical benefits, but 36 out of 55 patients showed some improvement, mostly in the early exudative and mixed cases.

The action of isoniazid seems to be mostly limited to the exudative element of the tuberculous process.

No demonstrable clinical, radiological, or bacteriological improvement was found when the dosage of isoniazid was increased from 4 to 8 mgm. per kilo of body weight. However, an accentuation in toxic manifestations was evident.

From a therapeutic standpoint, 4 mgm. of isoniazid per kilo of body weight provides an adequate concentration and satisfactory dosage.

Combined treatment with dihydrostreptomycin and isoniazid requires further studies before the advantages and limitations of such therapy can be properly evaluated.

It has been confirmed that an initial, natural or spontaneous as well as an acquired resistance to isoniazid exists and has to be considered in the treatment of patients.

Toxic symptoms are practically non-existant on a 4 mgm. per kilo of body weight dosage. These respond quickly to treatment and disappear when the drug is discontinued.

Although no increase in the total proteins of the blood was found, an elevation of the globulin fraction and inversion of the albumen-globulin ratio was observed in 14 patients, for which we have no satisfactory explanation.

Isonicotinic acid hydrazide is an effective drug in the treatment of pulmonary tuberculosis. Further studies toward solving the many therapeutic problems arising from its use should be continued.

RESUMEN Y CONCLUSIONES

Sesenta y dos casos de tuberculosis pulmonar activa, tratados con la hidracida del ácido isonicotínico por periodos de 90 a 297 días se relatan aquí. Se proporcionó la droga a la dosis de 4 miligramos y 8 mg. por kilo de peso.

Veintiseis recibieron la terapéutica combinada con isoniacida y estreptomicina. A pesar del pequeño número de casos, se considera que algunos de los resultados, son significativos.

Los síntomas generales de la tuberculosis desaparecieron en dos a tres semanas, bajando la temperatura a la normal, con un aumento considerable de peso y desarrollo de apetito voraz.

La tos y la expectoración, se eliminaron por completo. De 32 casos con esputos positivos, que se trataron con isoniacida, 16 viraron a la negatividad. De 21 positivos que recibieron la combinación de estreptomicina e isoniacida, 10 viraron. Los virajes fueron más frecuentes en los casos exudativos recientes y en los mixtos.

Todas las lesiones laríngeas y endobrónquicas respondieron favorablemente.

Los cambios radiológicos no fueron tan impresionantes como los clínicos, pero 36 de 55 enfermos, mostraron alguna mejoría, principalmente en el grupo de los exudativos recientes y en los mixtos.

La acción de la isoniacida, parece limitarse al componente exudativo del proceso tuberculoso.

No se pudo encontrar mejoría clínica, radiológica o bacteriológica más acentuada cuando se usaron 8 mg. en lugar de 4 por kilo de peso. Sin embargo, se notó una acentuación de la toxicidad.

Desde el punto de vista de la terapéutica, 4 miligramos por kilo de peso, proporcionan una adecuada concentración y satisfactoria dosificación.

La terapéutica combinada con dihidroestreptomicina e isoniacida, requiere más estudio antes de que las ventajas y las limitaciones de tal combinación, puedan estimarse de modo adecuado.

Se ha confirmado que una resistencia ya sea espontánea o adquirida a la isoniacida, tiene que considerarse en el tratamiento.

Prácticamente no hay síntomas tóxicos a la dosis de 4 mg. por kilo. Las manifestaciones tóxicas desaparecen rápidamente cuando la droga se suspende.

Aunque no se encontró aumento alguno en las proteínas totales de la sangre, se observó en 14 pacientes, una elevación de la fracción de la globulina y una inversión de la relación albúmina globulina para cuyo cambio no hubo explicación satisfactoria.

La hidracida del ácido isonicotínico, es una droga efectiva en el tratamiento de la tuberculosis pulmonar. Estudios ulteriores tendientes a resolver los múltiples problemas que emanan de su uso, deben continuarse.

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A Controlled Study of Isoniazid and Iproniazid*

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Studies of isoniazid and iproniazid were begun in March, 1952 at the Municipal Tuberculosis Sanitarium of Chicago. More than 500 patients have been treated. This report of the findings is given at the end of 18 months of experience. Comparisons were carried out with streptomycin and para-aminosalicylic acid and also with placebos as controls.[1-3]

General Methods: All patients had bacteriologically verified pulmonary tuberculosis. About 75 per cent were classified as far advanced. Forty-two per cent were negroes. Both sexes were equally represented. Evaluations of results were obtained in an unbiased manner because physicians did not know which patients received isoniazid and which received other therapy.

The groups studied are described as "Projects" A to E. Projects A, B, and C consisted of retreatment patients who had been in the sanitarium for considerable periods of time and had previously received much chemotherapy, usually in interrupted courses. Projects D and E consisted of initial therapy patients newly admitted to the institution.

Project A consisted of 110 adult patients, all of whom had bilateral pulmonary tuberculosis with demonstrable cavitation. All were afebrile and ambulatory. Alternate patients received isoniazid, 100 mgm. three times daily; the others receiving a placebo for the first four months of observation. After this period, the control cases also received isoniazid in the same dosage for the remainder of the study period from March, 1952 to March, 1953.

Project B consisted of 100 patients, similar to the above except that demonstrable cavitation was not required. Alternate patients were placed on iproniazid, 50 mgm. three times daily, and the remainder received a placebo. The placebo was discontinued after four months of study but the iproniazid was continued for a total of six months.

Project C consisted of 153 patients who were very ill or terminal. Eighty-six were started on isoniazid, 100 mgm. three times daily, in March, 1952 and followed to the present time. An additional 26 similar patients were started during subsequent months. Fifteen with amyloidosis and 26 with diabetes were also treated in this group whose general description is similar to the above.

Project D consisted of 146 newly admitted patients previously untreated. Alternate patients received isoniazid, 100 mgm. three times daily; the other group was treated with streptomycin, 1 gram twice weekly, and para-aminosalicylic acid, 12 grams daily.

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Project E was made up of newly admitted patients organized in the same manner as the preceding group, and admitted subsequently, beginning in October, 1952. Alternate patients received streptomycin and para-aminosalicylic acid as above; the others received all three drugs in the same dosage.

RESULTS

Weights

Project A: Forty-seven finished the four-month course of placebo therapy with an average weight gain of 1.8 pounds. The 27 of the group who gained weight had an average gain of 6.5 pounds.

Of the 44 who finished four months of therapy with isoniazid alone, the average weight gain was six pounds. Thirty-five gained weight, with an average of 8.8 pounds.

After one year of observation, the original placebo group had received eight months of isoniazid therapy. Of the 34 remaining in this group, 29 gained weight and five lost. The average weight gain for the entire group was 8.8 pounds. One patient lost 31 pounds because of a mental disturbance.

Of the alternate group who remained on isoniazid therapy for one year, 33 had an average weight gain of 10.1 pounds. Twenty-nine gained and four lost weight.

Project B: The average gain for 38 who remained on iproniazid for four months was 14.8 pounds. Of the 26 control patients who finished four months of placebo therapy, the average gain was 2.6 pounds.

Project C: Some of the patients in this group were bedfast and could not be weighed. The average weight gain of 75 who received four months of isoniazid therapy was 8.9 pounds. After one year of treatment, the average weight gain of the 50 remaining patients was 14.1 pounds.

Project D: In 49 who finished four months of isoniazid therapy, the average weight gain was 19.6 pounds. In the alternate streptomycin-para-aminosalicylic acid group, 51 gained an average of 15.3 pounds.

After eight to 11 months of therapy, the isoniazid group (28 remaining) gained an average of 22 pounds. In the alternate group (34 remaining), the average weight gain was 18 pounds.

X-Ray Results

X-ray film changes were classified as follows: (1) worse, (2) the same, (3) slight improvement, (4) moderate improvement, and (5) marked improvement. The total of those showing moderate plus marked improvement was considered significant and is used below in comparing the various groups. A great contrast is noted in the percentage of significant improvement of the retreatment groups as compared with the initial therapy groups.

Project A: Fifty-two patients on placebo therapy revealed 3 per cent significant improvement after four months. Forty-seven on isoniazid for the same period of time revealed 4 per cent significant improvement. Of 73 who completed eight months of isoniazid, 14 per cent showed significant

improvement. Ten per cent of 33 who finished one year of isoniazid fell in the same category.

Project B: At the end of four months of therapy, significant improvement occurred in 3 per cent of the placebo group and 4.5 per cent of the iproniazid group.

Project C: At four months, 77 revealed 2 per cent significant improvement. At 12 months, of 49 patients, 10 per cent, and at 18 months, of 41 patients, 6 per cent revealed the same degree of improvement.

Project D: After four to 12 months, the following percentages of significant improvement occurred: Of 71 on isoniazid, 56 per cent; and of 71 on streptomycin and para-aminosalicylic acid, 62 per cent.

Project E: After four to 12 months, 87 per cent of 48 on all three drugs revealed significant improvement. Of 57 on streptomycin and para-aminosalicylic acid, after the same period of time, 77 per cent showed the same degree of improvement.

Bacteriology

Three consecutive 24-hour concentration tests became negative in about two-thirds of the patients on isoniazid for six to 12 months. Those on streptomycin and para-aminosalicylic acid did equally well. Three consecutive negative cultures were obtained in 66 per cent of those remaining in Project A for one year.

Mortality

Project A: Of the 110 who started this project, six were dead after 12 months and seven after 18 months. During the first four months, one died while on placebo therapy; none on isoniazid.

Project B: None on this project died during the six months of observation.

Project C: Of the original 86 very ill and terminal patients who started this project, 10 were dead at the end of one year and 15 at the end of 18 months. Five of 15 amyloid patients were dead at the end of one year and two of 26 diabetics. Three out of 26 subsequently started patients in the same group were dead at the end of one year.

Project D: The period of observation varied from 11 to 18 months in this project. Of 77 treated with isoniazid, five were dead at the end of this time and, of the same number treated with streptomycin and para-aminosalicylic acid, three were dead.

Project E: The period of observation varied from five to 11 months on this project. None of the 67 treated with all three drugs died during the period of observation. One of the 74 on streptomycin and para-aminosalicylic acid died.

Toxicity

Isoniazid: Two patients developed reactions which were serious and might be attributed to the drug. The first was a female whose white cell count fell from 7,000 to 4,000 per c.ml. with neutrophiles diminishing from 3,000 to 2,000. This persisted for about two months while she was on isoniazid, then gradually returned to normal while therapy was continued. The second was a white male of 36 years, who had Jacksonian epilepsy

for many years and had been taking phenobarbital for one and one-half years prior to the present treatment. He developed neutropenia after two months of isoniazid. Both the isoniazid and the phenobarbital were discontinued at this time. The white cell count continued to fall, however; the lowest level being 1,500 per c.mi. The patient's condition became progressively worse in spite of supportive measures, including 12 blood transfusions, and death occurred about three and one-half months after medication was discontinued. Just prior to death, the white blood cell count rose to 36,000 per c.mi., of which 95 per cent were mononucleated cells. In spite of blood marrow studies and autopsy, the diagnosis remained doubtful.

Other types of toxicity were negligible in number and severity.

Iproniazid: Of 50 patients started, 22 developed one or more symptoms; 15 complained of dizziness upon arising from a supine position. Other complaints were severe headaches, numbness of the hands and feet, drowsiness, ataxia, and muscular twitching. Most of the complaints occurred during the first 10 weeks of therapy and disappeared thereafter.

Tuberculin tests: These were performed at the beginning and end of four months of isoniazid in 17 and, at the same interval, in seven of the placebo group in Project A. Simultaneous intradermal injections of 0.05 ml. of old tuberculin in dilutions of 1 to 1,000,000, 1 to 100,000 and 1 to 10,000 were given. After 72 hours, the transverse diameters of palpable indurations were measured. Changes in sensitivity were minor in both the placebo and isoniazid treated patients.

Liver function tests were performed on 15 patients in Project C, at the beginning and after nine months of treatment. Cephalin flocculation, thymol turbidity, blood proteins (including albumen, globulin and fibrinogen), bromsulphalein, cholesterol, and esters determinations were performed. No significant changes were noted.

Blood counts including differentials were carried out before, during, and after the first four months of treatment in 45 patients on isoniazid and 48 on placebo (Project A). No important changes were noted. Sedimentation rates decreased in twice as many on isoniazid as placebo in the same period.

Comment

Retreatment patients: It is obvious that isoniazid fails to heal the patients in this group by roentgenologic and bacteriologic criteria. It should be noted that patients in this category constitute a selected group. They represent the accumulated failures of a much larger group. In general, the fact that they failed on previous therapy was due to the presence of so-called "irreversible" disease. "Irreversible" disease indicates the presence of necrosis of tissue but does not preclude the possibility of healing by sterilization of infection followed by connective tissue replacement. The failure of isoniazid to produce healing of the "irreversible" disease in this group, therefore, indicates that it does not sterilize the lesions. It has been demonstrated that isoniazid penetrates the caseous lesion freely.[4] Since it fails to produce healing in spite of concentrations which should be

effective, it appears probable that it is rendered ineffective locally, either by local physical or chemical inactivation or by physical or chemical protection of the bacilli against the drug.

Although isoniazid fails to produce healing in this group of patients, it does bring about definite benefits in a considerable proportion. Clinical improvement is common and bacteriological improvement occurs in some. Roentgenologic evidence of relapse seems to be rare. These factors in a small percentage may help in bringing the patient to definitive surgical treatment, and thus change the outcome.

In general, then, patients who have failed upon adequate streptomycin and para-aminosalicylic acid, fail also upon subsequent isoniazid. It seems probable that when the maximum effectiveness of one bacteriostatic drug has been exhausted, substitution of another bacteriostatic drug will cause no great improvement.

Initial therapy patients: No statistically significant differences were noted in the effectiveness of isoniazid as compared with streptomycin with para-aminosalicylic acid in the virgin groups of patients. Roentgenologic improvement was equal on each regimen. Gain in weight and improvement in symptoms seemed somewhat better on isoniazid. Statistically, failure to achieve good results on either regimen showed moderate correlation with long duration (over three years) of disease.

The excellent results obtained in the virgin group (about 75 per cent significant roentgenologic improvement) contrasts markedly with the poor showing (about 10 per cent) of the group which had received previous streptomycin and para-aminosalicylic acid therapy. Thus, the most important factors militating against a good result with isoniazid appear to be long duration of disease and failure on previous chemotherapy.

Relapse: In spite of the development of marked resistance to isoniazid, relapse has been rare during the period of one year of treatment. The large majority of patients maintained the improvement which reached its height during the first six months. Those who became worse and died were almost invariably terminal or extremely ill at the beginning of isoniazid therapy. The greatest mortality rate (33 per cent) occurred in the patients with amyloidosis, all of whom were considered hopeless.

Comparison of one, two, or three drugs: Isoniazid alone, streptomycin and para-aminosalicylic acid, or all three drugs produced essentially equal therapeutic results in our patients. Possible advantages of the use of all three drugs, such as a longer delay in the development of resistance or lower relapse rate may become evident after longer periods of treatment.

Iproniazid: No demonstrable difference was noted in the therapeutic results with iproniazid as compared with isoniazid. Toxic effects, however, were troublesome, especially during the early weeks of treatment. Use of the drug was, therefore, discontinued after six months of trial.

SUMMARY

Experience with isoniazid in pulmonary tuberculosis over a period of 18 months, involving about 500 patients, has indicated that the drug is

of approximately the same order of effectiveness as streptomycin and para-aminosalicylic acid. In newly admitted, previously untreated patients, the results have been excellent, about 75 per cent achieving moderate or marked clearing on roentgenograms. Among patients who had persisting disease after considerable streptomycin and para-aminosalicylic acid therapy, isoniazid achieved but little improvement as demonstrated by roentgenograms; however, symptomatic improvement occurred in this group and was maintained in the large majority throughout the period of observation. Spread of disease while on isoniazid was uncommon.

Toxic effects were negligible with isoniazid.

Results with iproniazid were approximately the same as with isoniazid, but toxic effects were common and troublesome.

RESUMEN

La experiencia con la isoniacida en la tuberculosis pulmonar, en un periodo sobrepasando 18 meses, incluyendo 500 enfermos, ha indicado que la droga es aproximadamente del mismo grado de efectividad que la estreptomicina y el ácido paraminosalicílico. En los de primera admisión, que no han sido tratados antes, los resultados han sido excelentes, pues aproximadamente 75 por ciento alcanzan a una limpieza moderada o marcada radiológicamente. Entre los enfermos que tenian enfermedad persistente, después de un tratamiento considerable con estreptomicina y PAS, la isoniacida logró pequeña mejoria según los roentgenogramas. Sin embargo, la mejoria sintomática ocurrió en este grupo y se mantuvo en la gran mayoria a través del periodo de observación. La diseminación de la enfermedad mientras se usó la isoniacida no fué común.

Los efectos tóxicos de la isoniacida, no fueron de tomarse encuenta.

Los resultados con iproniacida, fueron aproximadamente los mismos que con la isoniacida, pero los efectos tóxicos, fueron comunes y molestos.

RESUME

Les auteurs, après avoir fait l'expérience du traitement de la tuberculose pulmonaire par l'isoniazide pendant 18 mois sur environ 500 malades, ont constaté que le produit à une efficacité à peu près comparable à celle de la streptomycine et du P.A.S. Chez les malades nouvellement admis à l'Hôpital, et qui n'ont subi antérieurement aucun traitement, les résultats ont été excellents, environ 75% d'entre eux montrèrent un nettoyage radiologique modéré ou très important. Pour les malades dont les signes persistèrent après traitement prolongé par la streptomycine et le P.A.S. l'isoniazide n'apporta qu'une légère amélioration perceptible sur les radiographies; cependant, pour ce groupe, on nota une amélioration des symptômes qui se maintint dans la grande majorité des cas durant toute la période d'observation. L'aggravation de la maladie pendant le traitement par l'isoniazide fut extrêmement rare.

Les troubles toxiques dus à l'isoniazide furent négligeables.

Les résultats obtenus avec l'impronіazide furent approximativement les mêmes que ceux obtenus avec l'isoniazide, mais avec l'iproniazide des

signes d'intoxication furent souvent constatés et eurent des conséquences fâcheuses.

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The Therapy of Pulmonary Tuberculosis and Its complications by Thiosemicarbazone*

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Domagk is considered the pioneer of chemotherapy in tuberculosis with thiosemicarbazones. He studied, in cooperation with his collaborators, a large number of thiosemicarbazones developed by the chemists Behnisch, Mietzsch and Schmidt, has found that the 4-acetylaminobenzaldeyde-thiosemicarbazone was the most efficacious substance against the tubercle bacillus. This compound, according to Domagk's researches on cultures of tubercle bacillus of the human type on egg culture medium containing p-aminobenzoic acid, exerts a marked inhibitory effect on the growth of tubercle bacillus at 1:300,000 solution, whereas streptomycin under the same conditions, shows an inhibition value at from 1:50,000 to 1:100,000 and PAS at 1:5,000. The in vivo effect has been confirmed by Domagk in experimental tuberculosis in guinea pigs and rabbits.

The clinical application in humans of this drug began in Germany in 1947. Many thousands of patients suffering from various forms of pulmonary and extrapulmonary tuberculosis have been subjected to this treatment.

Clinical Material: 37 patients all female, aged 19-65 years

Appearance of illness prior to treatment: In six cases recent, one to six months; in eight cases, one year; in seven cases, two years; in five cases, three years; in 11 cases, four to eight years.

Temperature prior to treatment: In 18 cases high fever, maximum 40 degrees C.; in 16 cases moderate, maximum 38 degrees C.; in three cases normal temperature.

Clinical classification of pulmonary tuberculosis: In 34 cases progressive form, in three cases stationary.

Pathologic classification from the roentgenogram of the pulmonary process: In 15 cases mixed, with predominance of the exudative type; in 22 cases mixed, with predominance of the productive type.

Cavitary: Unilateral or bilateral in 35 cases.

Other forms of tuberculosis: Tuberculous laryngitis in nine, with intense local clinical symptoms and laryngologic findings ranging from oedema to ulcerations. Tuberculous bronchitis in three, presenting clinically excessive frequent spasmodic cough, with bronchoscopic findings consisting of ulcerated lesions located in the right main bronchus and the bronchi of the upper right and upper left lobes. Tuberculous enteritis in one case, present-

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ing the full clinical picture of intestinal tuberculosis but not verified by x-ray film due to the severity of the patients condition.

Dosage: It is apparent from this study that the daily dosage of 150 to 200 mg. is sufficient to act therapeutically and to be fairly tolerable to almost all patients. This daily dosage is reached progressively by administration of 25 to 50 mg. daily during the first week, 100 mg. the second week, 150 mg. the third week and finally 200 mg. The rhythm of the dosage necessitates special attention for each patient. In severe cases with intense toxic symptoms, according to the personal advice of Domagk, the initial dose must be 12.5 mg. (half tablet) and the dose of 150 mg. must be reached slowly having as criterion for the increase of the dosage both the therapeutic effect of the drug and its tolerance by the body; because should important toxic reactions arise, treatment must be discontinued promptly for a few days. When the effect of the medication is beneficial and the drug is well tolerated, treatment should be continued for months. The longest period for our patients who received the drug was over 223 days, with a maximum total dosage of 28 Gm.

Laboratory examination: During the course of treatment, in addition to the usual clinical observation the following laboratory examinations were performed monthly: (1) examination of the sputum smear or of the fasting gastric contents for tubercle bacillus; (2) chest roentgenogram; (3) complete blood count; (4) erythrocyte sedimentation rate determination; (5) urinalyses. As regards the chemical control of the hepatic function, besides the urobilinogen excretion in urine, the thymol turbidity and cephalin flocculation examinations have been made. Also the plasma protein content and the albumin-globulin ratio have been determined by laboratory tests prior and after end of treatment.

Results

Clinical observations: Improvement in seven cases. No change in 25 and worsening in one. Interruption of treatment in four. The clinical improvement in the seven above mentioned cases consisted of apyrexia, reduction of cough, decreased expectoration, disappearance of tachycardia and night sweats, and gain in weight. This symptomatic improvement does not appear immediately after the first days of treatment, as observed during streptomycin therapy, but after 10 to 30 days from the starting of chemotherapy. This slow effect, observed also by other authors is why the use of thiosemicarbazone is counterindicated for the treatment of miliary tuberculosis.

In all the cases of laryngeal tuberculosis an evident result was noted with complete disappearance of voice changes and dysphagia. The symptoms usually responded rapidly within the first 10 days of treatment and were accompanied by improvement of laryngeal lesions. The response of treatment of laryngitis was greater when it was followed by improvement in the pulmonary process.

In the three cases of tuberculous bronchitis a marked reduction of cough was noted. The bronchoscopic examination revealed from simple improvement to healing of endobronchial lesions.

In the one case of tuberculous enteritis the clinical improvement was apparent and the persistent pain and diarrhea showed an evident regression.

Laboratory data: Sedimentation rate of erythrocytes: In all cases with clinical improvement a fall of the erythrocyte sedimentation rate, sometimes considerable, was observed.

Sputum: Conversion from positive to negative for acid-fast bacilli oc curred in four cases. The negativity persists for three to four months.

X-ray changes: In five cases of the seven showing clinical betterment, improvement in the roentgenograms was also observed consisting of diminution and clearing of the perifocal reaction. The radiologic improvement was not so clearly evident as in similar streptomycin-treated cases. Clinical and radiological improvements were noted in relatively recent tuberculosis with predominance of the exudative type and with intense perifocal reactions. No changes were observed in forms of chronic fibro-ulcerative tuberculosis.

Toxic reactions: Digestive system: The most frequent symptoms were from the stomach during the conteben therapy such as anorexia, sometimes intense, discomfort and pain in the epigastric region, nausea and in some cases vomiting, which symptoms may disappear with the continuing of treatment, but when they persist and vertigo and headache are added to them, it is necessary to discontinue the medication. Treatment had to be interrupted with the appearance of the above mentioned symptoms in four cases. Skin and the conjunctiva: In eight patients conjunctivitis developed, rather uncomfortable, and generalized exanthems pruritic, macular or erythemathous or pruritus without exanthem. These toxic manifestations subsided by reducing the dosage and by the administration of antihistaminic drugs or after temporary interruption of the treatment.

Blood: Moderate hypochromic, haemolytic anaemia developed in seven cases. However, treatment was continued with reduced dosages and during the treatment the erythrocyte count became gradually almost normal. In two a fall of the total leucocyte count below 5,000 per cu.mm. was observed and after discontinuation of treatment the leucocyte count became shortly normal; but no true picture of granulocytopenia was noted, in spite of the opinion of some authors stating that this complication appears more often in women and is due to the toxic effects of the drug on the haematopoietic system. This complication, if it appears, is serious and necessitates immediate discontinuance of treatment.

Liver: In one case subicteric skin changes with vomiting and pain in the right hypochondric region was noted and disappeared very slowly when the medication was interrupted. In this case and in another the thymol turbidity was higher than five units. We do not believe that the daily dosage of 150 to 200 mg. is hepatotoxic. This opinion was confirmed by laboratory tests of the hepatic function made in most of the cases. The plasma protein content and the albumin-globulin ratio were not perceptibly changed.

Kidneys: Albuminuria was present in four cases without other findings.

Rather significant haematuria was found in one and in two aggravation of the preexisting pyelocystitis.

SUMMARY

The use of 4-acetylaminobenzaldehype-thiosemicarbazone in the treatment of pulmonary tuberculosis, applied particularly in the recent form with exudative lesions and in the acute relapsing forms, exerts some beneficial effect, particularly on clinical symptoms, exudative processes and perifocal reactions, little effect or none against chronic pulmonary tuberculosis.

The therapeutic efficacy of this drug is evident and clear in laryngeal as also in tuberculous bronchitis and enteritis.

The administration of the drug is not indicated for the treatment of miliary and meningeal tuberculosis because its effect is slow. It has not yet been fully investigated if thiosemicarbazone resistant bacilli developed during the treatment. Possibly the emergence of such resistant bacilli is slow. No conclusions have been drawn either if the combination of the drug with streptomycin delays the appearance of streptomycin-resistant bacilli.

The dosage for each patient should be individualized. As it is apparent from the present study the dosage of 150 to 200 mg. daily is therapeutically feasible and fairly well tolerated.

The toxicity of the drug with the reported dosages is not significant. In spite of this the treated patients should be under medical observation.

RESUMEN

El uso de la 4-acetilaminobenzaldeido-tiosemicarbazona en el tratamiento de la tuberculosis pulmonar aplicada particularmente en las formas recientes con lesiones exudativas y en las recaídas águdas ejerce algún efecto benéfico especialmente en los síntomas, en las reacciones exudativas y perifocales, pero ningún efecto o muy poco sobre la tuberculosis pulmonar crónica.

La eficacia terapéutica de esta droga es evidente y clara en la tuberculosis laringea, en la bronquitis tuberculosa y en la enteritis de ese origen.

La administración de esta droga no está indicada en las formas miliares y meningeas porque su efecto es lento.

No se ha investigado aún si se desarrollan bacilos resistentes a la tiosemicarbazona durante el tratamiento. Posiblemente la aparición de tales formas resistentes, es lenta. No se ha llegado a conclusiones respecto de si la combinación con estreptomicina retarda la aparición de resistencia a esta última.

La dosificación en cada caso, debe ser individual. Es evidente, según este estudio que la dosis de 150 a 200 miligramos al día es práctica terapéuticamente y bastante bien tolerada.

La toxicidad de la droga con las dosis referidas, no es significante. A pesar de esto, los enfermos tratados deben servigilados.

RESUME

Le 4-acétylaminobenzaldehyde-thiosémicarbazone, utilisé dans le traitement de la tuberculose pulmonaire, surtout dans les formes récentes à lésions exsudatives, et dans les rechutes à caractère aigu, à un effet favo-

rable, spécialement sur les symptômes cliniques, les processus exsudatifs, et les réactions périfocales. Par contre, l'effet est de peu d'importance ou nul sur la tuberculose pulmonaire chronique.

L'efficacité thérapeutique de cette drogue est évidente dans les atteintes laryngées, aussi bien que dans la bronchite et l'entérite tuberculeuse.

L'administration du produit n'est pas indiquée dans le traitement de la tuberculose miliaire et méningée, parce que son effet est lent. On n'a pas encore trouvé si une résistance au produit pouvait se développer au cours du traitement. Mais il est possible que l'apparition de bacilles résistants soit lente. On ne sait pas encore si l'association de ce produit à la streptomycine retarde l'apparition de la streptomycino-résistance.

La dose doit être adaptée à chaque malade. Il résulte de l'étude actuelle que la dose de 150 à 200 mmgr. par jour est efficace, et est bien tolérée.

Le produit, administré à de telles doses, ne se montre pratiquement pas toxique. Néanmoins, les malades en cours de traitement doivent rester sous contrôle médical strict.

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Disseminated Lymphoblastoma Resembling Pulmonary Tuberculosis: Temporary Dramatic Response to Nitrogen Mustard Therapy (Case Report)

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This case is presented because of the unusual clinical manifestations and response to therapy. The patient, E.H.R., a 52 year old white male, was apparently in good health until the first week in June 1949, when he suddenly became ill with chills, fever, and a severe pain in his right shoulder and arm. This pain gradually decreased in intensity, becoming dull in character, but generalized over his entire body. Physical examination at the onset was negative except for a fever of 102 degrees F. Penicillin and streptomycin were given by a local practitioner with no improvement, and early in July 1949 he was referred to another physician for more complete diagnostic studies.

Blood counts on two occasions revealed normal red blood cell counts, and white blood cell counts of 8,000 and 9,500 with normal differential distribution of cells. Blood smears for malaria, a blood serum agglutination test for undulent fever, a spinal fluid examination, and a fecal examination for ova were all reported as being negative.

X-ray studies of the gall bladder and gastrointestinal tract were within normal limits. A postero-anterior film of the chest made on July 20, 1949 was reported as showing a fine stippled appearance of the lung parenchyma of the entire left upper lung field with some coalescence of the individual lesions. There was a similar but not so extensive involvement of the right upper lung field.

On July 29, 1949 three small subcutaneous nodules, which apparently had appeared since the onset of the present illness, were discovered on the patient's anterior chest wall and right flank. The nodule located on the right flank was removed for pathological study and was reported to be a malignant lymphoma. The patient was transferred to the Baptist Memorial Hospital in Memphis on August 10, 1949 for further study and treatment.

Upon admission he complained of generalized aching pains, fever, limited visual acuity and a weight loss of approximately 10 pounds since the onset of his illness. Temperature was 101.8 degrees F. rectally, pulse rate 90 per minute, respiration rate 22 per minute and blood pressure 96/70.

The positive findings on physical examination were non-tender liver with smooth contour, enlarged three finger-breadths beneath the right costal margin, one small palpable lymph node located in the right axilla, and a tumor measuring 2 cm. in diameter located over the fourth right anterior rib in the mid-clavicular line.

Consultation with an ophthalmologist, Dr. James Stanford, revealed a dark cataract of the right eye with absence of the fundus reflex. The left retina was edematous and showed several patches of recent exudate.

Admission laboratory studies revealed normal urine, blood sedimentation rate of 26 mm. in the first hour, red blood cell count of 3,690,000 with 11 Grams of hemoblobin, white blood cell count of 6,200 with differential distribution of 71 per cent segmented neutrophiles, 4 per cent band forms, 21 per cent lymphocytes, 1 per cent large mononuclears and 3 per cent eosinophiles. The blood Kahn was negative.

X-ray films of the chest showed soft mottling in the upper half of both lung

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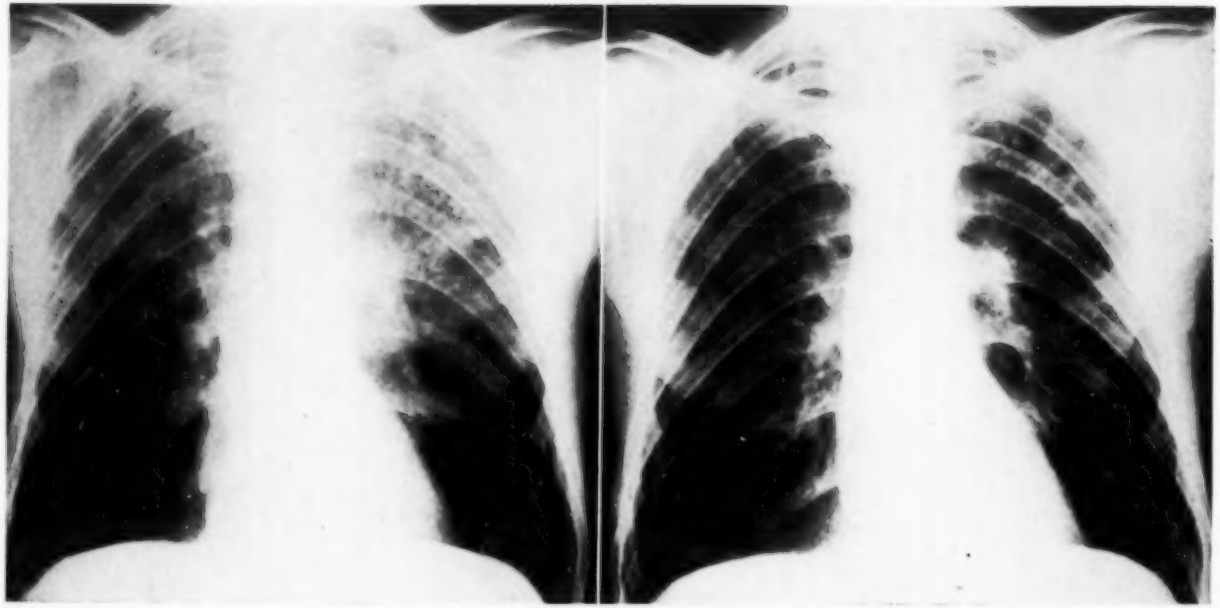

FIGURE 1

FIGURE 2

Figure 1: Mr. E.H.R., August 10, 1949. There is a fine stippled appearance of the lung parenchyma in the entire upper lung field on each side. This appears heaviest in the left. Biopsy of tumor on the right fourth anterior rib revealed a lymphoblastoma.—*Figure 2:* August 23, 1949. This film, made 13 days after the admission film shows almost complete clearing of the metastatic lymphoblastoma in each lung field. The patient received 10 milligrams of Methyl-bis intravenously on each of four consecutive days, with dramatic clinical improvement.

fields, suggesting "focal areas of edema with alveolar distribution." A bronchoscopic examination was performed on August 11, 1949, revealing normal larynx and tracheo-bronchial tree. A bronchial washing taken at the time of the examination was reported negative for acid fast bacilli, fungi, and tumor cells.

The tumor located on the fourth rib on the right anteriorly was removed and reported to be a lymphoblastoma by the pathologist, Dr. Merlin Trumbull.

Treatment with Methyl-bis (B-chloroethyl amine hydrochloride), one of the nitrogen mustard compounds, was started on August 13, 1949, 10 milligrams being given intravenously each day for four consecutive days. On the fourth day of treatment the patient's temperature returned to normal and he exhibited a marked symptomatic improvement, including an astonishing increase in his visual acuity.

Blood studies on August 18, 1949 revealed a red blood cell count of 2,460,000 with 8.3 Grams of hemoglobin and a white blood cell count of 3,600 with a differential distribution of 79 per cent segmented neutrophiles, 4 per cent band forms, 16 per cent lymphocytes, and 1 per cent eosinophiles. He was given a transfusion of 500 cc. of whole blood on each of the next three consecutive days. Blood studies on August 22, 1949 revealed correction of the secondary anemia but further reduction of the white blood cell count to 1,500 per cubic millimeter with differential distribution of 63 per cent segmented neutrophiles, 1 per cent band forms, 31 per cent lymphocytes, 2 per cent mononuclears, 1 per cent eosinophiles and 2 per cent basophiles.

Reexamination of the chest by X-ray film on August 23, 1949 showed almost complete clearing of the previously described infiltration of both upper lung fields. Deep x-ray therapy was considered as an adjunct to the Methyl-bis therapy. However, in view of the low white cell count it was considered advisable to wait for a period of two or three weeks. He was discharged to his home on August 24, 1949, markedly improved both symptomatically and clinically.

Telephone conversation with his son six weeks later revealed the fact that his improvement was of short duration. He was again hospitalized, this time in Little Rock, Arkansas, and was in poor condition with fever, weakness and almost total blindness.

SUMMARY

A patient with disseminated lymphoblastoma showed a brief but astonishing improvement under treatment with Methyl-bis (B-chloroethyl amine hydrochloride).

The pulmonary lesions closely resembled pulmonary tuberculosis, but cleared almost completely one week after treatment, only to recur again six weeks later.

RESUMEN

Un enfermo con linfoblastoma diseminado mostró una breve pero sorprendente mejoria bajo el tratamiento con Metil-bis (clorhidrato de B-Cloroetilamina).

Les lesiones pulmonares se parecian mucho a las de la tuberculosis, pero se aclararon completamente una semana después del tratamiento, para recurrir seis semanas después.

RESUME

Un malade atteint de lymphoblastomes disséminés montra une courte mais étonnante amélioration par le traitement au méthyl-bis (B-chloroethyl amine hydrochloride).

Les lésions pulmonares ressemblaient étroitement à celles de la tuberculose, mais disparurent presque complètement après une semaine de traitement, pour réapparaitre seulement six semaines plus tard.

Sterile Hemopneumothorax Due to Pulmonary Infarction

ALBERT V. MYATT, M.D.*
New Orleans, Louisiana

Sterile hemopneumothorax due to rupture of a pulmonary infarct has been reported infrequently. In 1947 Rawson and Cocke[1] were able to find only five cases reported. They added a sixth case. In 1949 Masson and Hartman[2] reported another case—the seventh.

Five of these seven reported cases were confirmed by autopsy. In all five proved cases heart disease with congestive failure was the primary disease. Report of an additional case—presumably the eighth—follows:

A 24 year old Negro male began to have dyspnea on exertion in 1948. As a child he had joint pains, but was never told that he had rheumatic fever. He served in the Army from 1943 to 1945 and had no illness.

In November, 1949 he was hospitalized at the U. S. Public Health Service Hospital in San Francisco, California, because of increasing dyspnea and cough. His heart was enlarged and a loud high pitched blowing systolic murmur was heard at the apex and transmitted to the axilla. A diastolic gallop rhythm was present. His blood pressure was 110/82 and pulse 112. Coarse moist rales were heard at the bases of his lungs. Electrocardiogram showed left ventricular hypertrophy. Chest x-ray film showed an enlarged heart. He improved with treatment and went back to work—taking digitalis leaf and using a low sodium diet.

He was hospitalized on two other occasions but continued to do light work as a porter until June, 1950. After that date he remained at home at rest. He continued to take digitalis and remained on a low sodium diet.

His final hospital admission was in October, 1950. He was acutely ill and in respiratory distress. He complained of marked dyspnea, hemoptysis and left upper quadrant abdominal pain. Blood pressure was 90/78. He appeared cyanotic. There was venous distension. The heart was enlarged; diastolic gallop rhythm and a loud apical systolic murmur were present. Over the left lung, loud coarse moist rales were elicited throughout. The right lung showed markedly reduced breath sounds, but the percussion note was equal to that on the left side. A bedside chest x-ray film revealed pneumothorax on the right with partial collapse of the right lung. Oxygen and other measures for acute heart failure were used but the patient died shortly after admission to the hospital.

Autopsy showed air and 500 cc. of bloody fluid in the right pleural cavity. The right lung weighed 825 grams and was atelectatic. There were multiple areas of infarction throughout the right upper and right lower lobes. They were hemorrhagic in nature and showed a sharp demarcation between the infarcted areas and the adjoining lung parenchyma. A sub-pleural infarction in the right upper lobe showed a tear which had allowed escape of air and blood into the right pleural cavity. The left lung also showed infarcts which were smaller and older than those in the right lung. The heart weighed 550 grams. The left ventricle was hypertrophied. There was dilatation of all chambers. The mitral ring was dilated, measuring 5.0 cm. in diameter. The spleen and kidneys showed old infarcted areas. The pulmonary infarcts apparently arose in the dilated chambers of the right heart.

*Surgeon, U. S. Public Health Service. USPHS Hospital, New Orleans, Louisiana.

SUMMARY

A case of sterile hemopneumothorax due to rupture of a pulmonary infarct is presented. The patient had rheumatic heart disease with congestive failure as the primary diagnosis. Only seven similar cases have been previously reported.

RESUMEN

Se presenta un caso de hemoneumotorax consecutivo a ruptura de un infarto pulmonar. El enfermo tenia enfermedad cardiaca reumática con insuficiencia congestiva como diagnóstico primario. Solamente se han referido siete casos similares previamente.

RESUME

L'auteur rapporte une observation d'hémo-pneumothorax stérile dû à la rupture d'un infarctus pulmonaire. Le diagnostic primitif fut celui de coeur rhumatismal, avec état congestif associé. Jusqu'à présent, il n'a été rapporté que sept observations comparables à celle-ci.

REFERENCES

1 Rawson, A. J. and Cocke, J. A.: "Infarction of an Entire Pulmonary Lobe with Subsequent Aseptic Softening Causing Sterile Hemopneumothorax," *Am. J. Med. Sciences*, 214:520, 1947.

2 Masson, J. M. and Hartman, S. A.: "Sterile Hemopneumothorax Caused by Softening and Perforation of a Pulmonary Infarct," *Dis. of Chest*, 16:42, 1949.

Chest Conference

DAVID T. CARR, M.D.*
Rochester, Minnesota

There are many approaches to the problem of teaching in medicine. Obviously, the teaching method must be varied to suit the subject matter, the students, the available case material, and the teachers. One of the most useful and effective methods is the interesting case conference. Such a conference has been conducted weekly for several years at the Mayo Clinic by those physicians particularly interested in diseases of the chest. This type of conference has met with the enthusiastic approval of many visiting physicians, fellows of the Mayo Foundation, and members of the staff of the Mayo Clinic.

Although the conference is administered by the medical section on diseases of the chest, it is a joint activity of the members of that department, the thoracic surgeons, the surgical pathologists, the bacteriologists, the radiologists, and the physiologists. As many of these as possible attend each conference and the opportunity to have each case discussed from various points of view has been of great value. Scheduling the conference at a time which was convenient for so many men was not easy and made it necessary to meet each Thursday at 7:30 a. m. The conference is planned especially for the consultants and fellows of the sections interested in diseases of the chest, but is open to all interested physicians and in spite of the early hour, the average attendance is 100 to 125 men.

Cases are selected for presentation by any consultant and are usually chosen from current clinical material, so that current ideas of diagnostic study and treatment will be illustrated. In our experience it has been more satisfactory to present cases with proved diagnoses.

The actual presentation of the case is usually made by one of the fellows, who summarizes the patient's history, physical findings, and routine laboratory studies. The moderator, who is usually one of the medical consultants, then calls on various fellows and consultants for opinions concerning the patient's problem and how to solve it. Results of special studies are given as requested. Special consultants are asked for their opinions about special aspects of the case and each discussant is requested to commit himself as to diagnosis and recommended treatment. Each man present is free to ask questions, to make comments, or to challenge another's comments or opinions. This part of the conference is very informal, but the moderator conducts it in such a way that the maximal teaching value is obtained from each case. This is accomplished by asking leading questions, demanding explanations, and suggesting alternative diagnoses—even wrong ones.

*Division of Medicine, Mayo Clinic, Rochester, Minnesota.

The eighth in a series of articles prepared under the sponsorship of the Council on Undergraduate Medical Education of the American College of Chest Physicians.

However, this is done in a kind, friendly manner avoiding the embarrassment of anyone. This informality inevitably leads to some good-natured bantering and even some "needling" and this has made the conference entertaining as well as instructive.

When the general discussion has been completed, the consultant presenting the case gives a brief comment about the correct diagnosis, how it was proved, and the treatment that was advised. Further comments and questions are then permitted. Such a case presentation requires 15 to 25 minutes, so that three or four cases can be presented at each conference, which lasts one hour.

We have not found it worthwhile to bring either the patient or pathologic specimens to the conference. However, in selected cases photographs of patients, or specimens or photomicrographs have proved of value.

Editorial

FIFTIETH ANNIVERSARY OF THE NATIONAL TUBERCULOSIS ASSOCIATION

This month the National Tuberculosis Association celebrates its 50th anniversary. The accomplishment in tuberculosis control over the brief period of 50 years far exceeds the fondest dreams of those who founded the Association.

It is fortunate that a physician who so thoroughly comprehended the magnitude of the tuberculosis problem and with such a clear vision of the needs for its control should have been elected first president. Dr. E. L. Trudeau's President's Address embodied all of the important procedures, the use of which over the decades has proved his vast understanding of this disease. His address, delivered in Washington, D. C. on May 18, 1905, remains a classic in tuberculosis literature. He said, "It is evident that if every man and woman in the United States were familiar with the main facts relating to the manner in which tuberculosis is communicated and the simple measures necessary for their protection, not only might we reasonably expect as a direct result of this knowledge a great diminution in the death rate of this disease, but the people would soon demand and easily obtain effective legislation for its prevention and control."

Education became and has continued to be the main activity of this organization. It resulted in provision of sanatoriums in unbelievable number within the next two decades, in early diagnosis campaigns and numerous other activities. It was helpful to the United States Bureau of Animal Industry and its affiliated state organizations, including veterinarians everywhere in its phenomenal accomplishment in the control of tuberculosis among domestic animals.

The educational campaign of the national, state, municipal and county tuberculosis organizations has resulted in the public having more information about tuberculosis than any other disease. One of the main objectives of educational work was to prevent the loss of life from tuberculosis. In 1904 the mortality rate closely approached 200 per 100,000 people. If this rate had been allowed to obtain, we would now have about 300,000 deaths annually. Instead, the mortality rate has been reduced to 16.1 per 100,000 in 1952, with a total of approximately 25,000 deaths.

With the decrease in mortality, there has been a corresponding reduction in morbidity and infection attack rates. In a number of states the mortality rate is now less than 10 per 100,000, and in some with populations of three million or more the rate is in the neighborhood of six.

The accomplishment during the past 50 years is so remarkable that such a sense of false security has developed, even among many tuberculosis workers, that effort is being relaxed and funds are being diverted to non-tuberculous conditions. The National Tuberculosis Association can stem the tide, but it must be done quickly before the support of our 160 million

people dwindles. It would be exceedingly unfortunate if effort should continue to be relaxed when it really needs to be intensified. The battle against tuberculosis is not half won. Most of the effort to date has been directed against gross disease which causes symptoms, liberates tubercle bacilli or casts x-ray shadows. This has been important and should be continued for some time, but it will be necessary to shift emphasis to the tubercle bacillus rather than just the gross lesions it produces.

This can be done with uncanny accuracy by the tuberculin test, but it is a Herculean task. There has been no time in history when a nation has been so prepared to perform such a task. If it is not done now because of diminishing interest and effort, it probably will never be done. It is unlikely that such organization and machinery with such highly qualified personnel as is now available to carry through to the eradication of tuberculosis will ever again be duplicated.

Testing all persons from a few weeks after birth to senility will reveal the locations of practically all tubercle bacilli in this country. They will be found holding forth in the bodies of about a third to a fourth of the population, for the most part in older people. Methods are now available to prevent these tubercle bacilli from leaving their present habitats. This involves careful periodic examination of all who harbor tubercle bacilli as long as they live. This is the only method yet known by which eradication of tuberculosis is possible. It will require the lifetime of workers for several generations and will tax every facility of tuberculosis organizations.

The National Tuberculosis Association will not have attained the goal for which it was organized and toward which it has gone nearly half way until eradication of the tubercle bacillus is accomplished. Despite the magnitude of this problem it is not too great to ultimately be solved by the National Tuberculosis Association and its allies.

J. A. MYERS.

The President's Page

COLLEGE COUNCILS AND COMMITTEES

This is the third in a series of messages which have been appearing in our Journal. The first and second articles appeared in the March and April issues and I trust that you have had an opportunity to read them. I would appreciate very much having your comments as well as your recommendations.

One of the most important aspects of our College is the activities of the many councils and committees to which are delegated the responsibility of putting the College program into effect.

The College program is built on a triad comprising: (1) Medical Education; (2) Public Health; (3) Research.

Under the first classification are the Council on Undergraduate Medical Education and Council on Postgraduate Medical Education. The Council on Undergraduate Medical Education has been in existence for 18 years. This Council has cooperated with medical schools to improve the teaching of diseases of the chest, conducted numerous surveys of undergraduate medical education, and published many reports concerning its activities, including a book entitled THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS (Charles C. Thomas Company). A companion book entitled NON-TUBERCULOUS DISEASES OF THE CHEST with 36 contributors, is now in press and will be available at an early date. During the past months, a series of articles on "The Teaching of Chest Disease in Medical Schools" has been appearing in the Journal and I trust that you have read these interesting articles.

The Council on Postgraduate Medical Education has been functioning for the past eight years. During this period, 44 postgraduate courses covering the broad aspects of cardiovascular and pulmonary diseases have been presented in various parts of the country. There have been 2,542 physicians from every state in the Union and many other countries enrolled in these postgraduate courses. In addition, several hundred of our Fellows and invited guests have lectured at the courses. These excellent postgraduate courses have been widely publicized and highly praised. Many medical societies have sought consultation with our Executive Director to obtain information concerning the successful management of the College postgraduate courses.

Another phase of our postgraduate program has been the establishment of a "Speakers Bureau" and arrangements have been made for many of our Fellows to lecture at College Chapters throughout the world. The Committee on Resident Fellowships has been instrumental in bringing physicians from various countries to the United States for postgraduate training. At the present time, there are 18 physicians from 15 countries in training.

The Committee on Audiovisual Aids is another important adjunct to our postgraduate activities. Motion picture sessions are presented at national and international meetings of the College and at Chapter meetings throughout the world.

Under the second classification are the Council on Public Health and Council on Hospitals. A number of committees serving under the direction of these councils are conducting a multitude of surveys and investigations. The Council on Public Health and its committees are responsible for the organization of committees on tuberculosis, cardiovascular disease, and diseases of the chest in the state and county medical societies. One of the committees is concerned with routine chest x-ray in general hospitals and mass chest x-ray surveys.

For the past four years, the College Committee on Chest X-ray has met regularly with the American College of Radiology and many decisions to clarify mass x-ray surveys have emanated from this joint effort. Another important committee has been organized with the Industrial Medical Association to discuss industrial chest

disease. Recently the American Trudeau Society was invited to appoint a committee to participate in this joint effort.

The Council on Hospitals and its many important committees are reporting their activities in "The Hospital Counselor" which I trust is reaching you at regular intervals. The editor of this splendid publication will, I am sure, be pleased to have your comments.

The third and a most important part of this triad is the Council on Research. The Council and its numerous committees are concerned with every aspect of diseases of the chest. Many of the committees have carried on investigations in their related fields and a number of their reports have appeared in our Journal, while others have been discussed at College conferences and meetings.

All of the councils and committees meet annually at the time of our Annual Meetings and all members of the College are encouraged to attend these meetings.

Alvin E. Foster

20th Annual Meeting

American College of Chest Physicians

The 20th Annual Meeting of the College will be held at the Fairmont Hotel, San Francisco, June 17 through 20. The scientific program to be presented was published in the April issue of *Diseases of the Chest* and on the following pages of this issue of the journal some additional information is given concerning various sessions planned for the meeting.

Motion Picture Session on Diseases of the Chest

An interesting program of motion picture films on diseases of the chest will be presented at the 20th Annual Meeting of the College in San Francisco. The film session will be presented at 8:00 p. m. on Friday evening, June 18, at the Fairmont Hotel, and has been arranged by the Committee on Audiovisual Aids of the American College of Chest Physicians. Dr. Paul H. Holinger, chairman of the Committee, will preside at the session. The following films will be presented:

"Surgical Treatment of Mitral Stenosis,"
Charles P. Bailey and Houck E. Bolton, Philadelphia, Pennsylvania.

"Pneumonectomy for Bronchiectasis,"
Evarts A. Graham, St. Louis, Missouri.

"Degenerative Lung Disease,"
Gerald C. Crenshaw, Oakland, California.

"Electrocardiographic Study of Coronary Artery Disease,"
Myron Prinzmetal, Los Angeles, California.

"Clinical Application of a New Method of Mechanical Coughing Exsufflation with Negative Pressure,"
Alvan L. Barach, Gustav J. Beck and William Smith, New York City.

"Repair of Hernia of the Lung,"
Lawrence M. Shefts, San Antonio, Texas.

"Extraperiosteal Lucite Ball Plombage,"
Francis M. Woods, Brookline, Massachusetts.

Council on Hospitals to Hold Open Forum at 20th Annual Meeting of the College

The Council on Hospitals of the American College of Chest Physicians will hold a meeting at the Fairmont Hotel, San Francisco, at 2:00 p. m. on Thursday, June 17. The committees on Standards and Accreditation, Rehabilitation, Hospital Statistics, Chest Diseases in Institutions, and Psychosomatic Aspects of Diseases of the Chest, which serve under the Council on Hospitals, will participate in this conference.

At 4:00 p. m. an open meeting of the Council on Hospitals will be held, at which time the following program will be presented, presided over by Dr. R. S. Anderson, chairman:

"The Changing Trends in Tuberculosis Hospitals,"
Chesley Bush, Acting Chief, Bureau of Tuberculosis Control, California Department of Public Health, San Francisco.

Question and Answer Period of Medical Administrative Problems:

Panel: Robert J. Anderson, Assistant Chief, Division of Special Health Services, U. S. Public Health Service, Washington, D. C.

Otto L. Bettag, Director, Department of Public Welfare, State of Illinois, Chicago.

Chesley Bush, San Francisco, California.

Buford Wardrip, Medical Director, Alum Rock Sanatorium, San Jose, California.

Members of the Council:

R. S. Anderson, Erie, Pennsylvania, Chairman
Leonard C. Evander, Lockport, New York, Vice-Chairman
P. J. Sparer, Memphis, Tennessee, Secretary
Carl H. Gellenthien, Valmora, New Mexico, Regent Advisor
Otto L. Bettag, Chicago, Illinois
I. D. Bobrowitz, Otisville, New York
Charles A. Brasher, Mt. Vernon, Missouri
James T. Duncan, Livermore, California
Ralph Horton, Oneonta, New York.

All physicians interested in medical administrative problems are cordially invited to attend this meeting and participate in the discusson.

LADIES ACTIVITIES

THURSDAY, JUNE 17

Tea and Reception — Mark Hopkins Hotel

The Tea and Reception will be given in honor of Mrs. Alvis E. Greer and Mrs. Edward W. Hayes, the wives of the President and first Past-President of the College.

FRIDAY, JUNE 18

Luncheon — Allied Arts, Stanford University, Menlo Park

The ladies will be taken to Stanford University by bus and then to Menlo Park where a luncheon will be served at the Allied Arts, which is partially manned by volunteers and proceeds donated to the Stanford Convalescent Home. The craftsmen of the area display and sell their work of art here.

After lunch there will be a visit to Sunset House, the model home and garden maintained by the publishers of Sunset Magazine. The recipes which they publish are tested here and their horticultural ideas are presented.

SATURDAY, JUNE 19

Annual Convocation (Formal)

Cocktail Party

Sponsored by Panray Corporation, New York City.

Annual Presidents' Banquet

Dancing and Entertainment

Sponsored by the California Chapter, American College of Chest Physicians.

The above functions will be held at the Fairmont Hotel.

SUNDAY, JUNE 20

Brunch — St. Francis Yacht Club, Yacht Harbor

Some of the ladies may be interested in taking the Bay boat excursion, a one hour trip, leaving Fisherman's Wharf at frequent intervals.

The Ladies Reception Committee will have private cars available to take the visiting ladies on personalized tours of such places as the Planetarium, the Tea Garden, museums, etc.

LADIES RECEPTION COMMITTEE

Mrs. Alvis E. Greer, Honorary Chairman
Mrs. Edward W. Hayes, Honorary Chairman
Mrs. John J. Sampson, General Chairman

Co-Chairmen

Tickets and Arrangements
Mrs. Thomas B. Wiper

Registration
Mrs. Martin J. Seid

Events
Mrs. Shirley H. Baron
Mrs. Mortimer A. Benioff
Mrs. A. Lincoln Brown
Mrs. William L. Rogers
Mrs. Edgar Wayburn

Mrs. Morrison H. Belmont
Mrs. Fred C. Blake
Mrs. William A. Cassidy
Mrs. Gerald L. Crenshaw
Mrs. Lloyd B. Dickey
Mrs. David J. Dugan
Mrs. Seymour M. Farber
Mrs. Fred Firestone
Mrs. John L. Gompertz
Mrs. James O. Greenwell, Jr.
Mrs. H. Corwin Hinshaw
Mrs. Charles L. Ianne
Mrs. James Kieran
Mrs. Paul C. Samson
Mrs. Sidney J. Shipman
Mrs. Harold G. Trimble
Mrs. William C. Voorsanger

MEETING AT MEXICAN INSTITUTE OF CARDIOLOGY

A series of lectures will be given at the Mexican Institute of Cardiology, Mexico City, under the direction of Dr. Ignacio Chavez, Director of the Institute. The lectures will be given for a visiting group of members of the American College of Physicians. Dr. Donato G. Alarcon, Regent of the College for Mexico, will present a lecture on "The Importance of Tomography in the Diagnosis of Chest Diseases." Both Drs. Chavez and Alarcon will present papers at the annual meeting of the American College of Chest Physicians in San Francisco and Dr. Chavez will be made an Honorary Fellow of the College at the meeting.

College Chapter News

PUERTO RICAN CHAPTER

A meeting of the Puerto Rican Chapter of the College was held recently at which time the following officers were elected:

Pedro J. Durand, San Juan, President
Hector Martinez-Villafane, Santurce, Secretary-Treasurer

Dr. Jaime F. Pou, Hato Rey, is Regent for Puerto Rico and Dr. E. Martinez-Rivera, Hato Rey, is Governor.

SOUTH INDIA CHAPTER

The South India Chapter of the College was organized on January 29 in Madras. Officers elected are: Dr. P. Arunachalam, Madras, President; and Dr. D. Damoder Das, Madras, Secretary-Treasurer. Dr. K. S. Sanjivi of Madras, Governor of the College for South India, participated in the organization of the chapter. A clinical meeting under the joint auspices of the Indian Thoracic Society and the American College of Chest Physicians was held in the Common Hall, Madras Medical College, at which time a scientific program on the surgical and clinical aspects of diseases of the chest was presented. Dr. Raman Viswanathan of New Delhi is Regent of the College for India.

CUBAN CHAPTER

The Cuban Chapter held its annual meeting in February in Havana. Plans for a postgraduate course on diseases of the chest were discussed. (See announcements, page xxiii. The following officers were elected:

Hilario Anido y Fraguio, Havana, President
Leopoldo Araujo y Bernal, Havana, Vice-President
Servio Caroll y del Valle, Havana, Secretary-Treasurer

QUEBEC CHAPTER

New officers of the Quebec Chapter of the College, elected at their annual meeting in Montreal on February 26 are:

F. L. Phelps, Ste. Agathe des Monts, President
Georges Gregoire, Quebec, First Vice-President
Lasalle Laberge, Sherbrooke, Second Vice-President
M. Allan Hickey, Ste. Agathe des Monts, Secretary-Treasurer

Guest speakers at the meeting were Drs. Arthur Vorwald, Detroit, Michigan; William B. Tucker, Minneapolis, Minnesota; and John D. Steele, Milwaukee, Wis.

Dr. B. Guy Begin, Montreal, serves as Governor of the College for Quebec and Dr. Harold I. Kinsey, Toronto, Ontario, is Regent for Canada.

MINNESOTA CHAPTER

A business meeting of the Minnesota Chapter will be held at the time of the state medical society meeting in Duluth, June 7.

A. M. Olsen, Secretary.

ILLINOIS CHAPTER

A meeting of the Illinois Chapter was held at the St. Clair Hotel, Chicago, on April 16. "The Use of a Recording Oximeter in the Management of Postoperative Oxygen Therapy" was presented by Dr. Miguel Castellanos, Richard Thompson, A. B., Dr. William E. Adams, and Mr. Willard Weber, University of Chicago School of Medicine, and "The Treatment of Chronic Pulmonary Diseases with Intermittent Positive Pressure Breathing Methods" by Dr. R. Drew Miller, Mayo Foundation, Rochester, Minnesota.

College News Notes

Dr. Felix Baum, consulting physician in pulmonary diseases, Essex Mountain Sanatorium, Verona, New Jersey, and St. Mary's Hospital, Orange, addressed the medical staff of the Veterans Administration Hospital, Coral Gables, Florida, February 26 on "Intrathoracic Malignancies in Tuberculosis Institutions."

Dr. Hawley H. Seiler, Tampa, Florida, consultant in thoracic surgery, Veterans Administration Hospital, Passe-a-Grille, Florida, recently spoke before the Isthmian Canal Zone Medical Association meeting held in the Gorgas Memorial Laboratory in Panama City, Panama. His topic was "Thoracic Problems of General Interest." He also addressed the staff of the Gorgas Hospital on "Indications for Pulmonary Resection."

Dr. Burgess L. Gordon, Philadelphia, Regent of the College for Pennsylvania and President of the Woman's Medical College of Pennsylvania, presided over the Health Assurance Forum held in Philadelphia, March 11. College members on the forum were Dr. Anthony J. Lanza, New York City, moderator of the panel on "Preventive Medicine and Industry." Dr. Harold G. Trimble, Oakland, California, discussed "Going Back to Work," and Dr. Katharine R. Boucot, Philadelphia, discussed "Health Maintenance for Enhancing Labor-Management Accord."

IV CENTRAL AMERICAN CONGRESS ON TUBERCULOSIS

The IV Central American Congress on Tuberculosis was held in Panama City, at the Hotel Panama, November 30 - December 4, 1953, under the direction of Dr. A. Vicente Mastellari, Regent of the American College of Chest Physicians for Panama.

The Congress was attended by delegations from eight Central American countries and the United States and a scientific program dealing with the various aspects of tuberculosis was presented. The following members of the American College of Chest Physicians attended the Congress:

Miguel Iglesias, M.D., Cartago, Costa Rica
Luis Mungula Alonzo, M.D., San Jose, Costa Rica
Luis Roy, M.D., Port-au-Prince, Haiti
Miguel Jimenez, M.D., Mexico, D. F.
Herbert Mantz, M.D., Kansas City, Missouri (deceased)
J. B. Flors, M.D., Panama City
Jean Canavaggio, M.D., Panama City
Maximo Carrizo, M.D., Panama City
V. Avendano, M.D., Panama City
A. Arias, M.D., Panama City.

ULAST MEETING

Pictured above are officials of the College from the United States and Latin American countries at the meeting of the Council on Pan American Affairs of the College held in conjunction with the Tenth Congress of the Union of Latin American Tuberculosis Societies, Caracas, Venezuela, December 5-10, 1953.

BOOK REVIEWS

The book "Managing Your Coronary" by William A. Brams, is a short, small book on coronary thrombosis or occlusion. It is well written. It is presented in simple, direct, forceful language. The author cites many illustrations and gives clear explanations. He defines modern methods of treating a patient with coronary thrombosis, for example, as to length of time in bed, returning to work and rehabilitation. Altogether, he sounds an optimistic note. The book is void of boring, morbid statistics, and as far as it goes, it is good for the patients and lay people in general. The doctor will still have to be the mainstay of treatment, of course. The book hardly enters into specific treatment but perhaps this is wise.

ARTHUR M. MASTER, M.D.

Inhalation Therapy and Resuscitation, by Meyer Saklad, M.D.

This is a textbook that fills the need for a great number of physicians who are interested in this very vital phase of therapy. It has an advantage over most textbooks on this subject in that he deals with the basic pharmaco-physiology in careful and concise detail. His classification of hypoxia is one of the finest.

The discussions of the various pathologic conditions are direct and of sufficient length to give one a background to the therapy. His discussions are those of a man well versed in the subject who has not only the basic scientific data, but a wealth of experience in the management of these conditions. The book is amply illustrated and edited in an excellent fashion. It is a book that can be recommended wholeheartedly to all who are interested in inhalation therapy and the ever present problem of resuscitation.

MAX S. SADOVE, M.D.

MEDICAL SERVICE BUREAU

POSITION WANTED

Experienced chest specialist and administrator with outstanding qualifications desires medical directorship or superintendency. Graduate of Class A American medical school. Excellent references from chest specialists of national repute. Please address all inquiries to Box 284B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

ANNOUNCEMENTS

The University of Groningen (Netherlands) will present a postgraduate course on the fundamentals of thoracic clinical science and surgery, June 8-29, 1954, at the university. For information, please write to Prof. Dr. R. Brinkman, Modder-manlaan 21, Groningen, Netherlands.

Three postgraduate courses in Pediatric Cardiology will be presented by Drs. Benjamin M. Gasul and Egbert H. Fell and associates, at the Cook County Graduate School of Medicine, Chicago, Illinois. The courses will be intensive and practical, and are designed for the pediatrician, internist, general practitioner and roentgenologist. For complete information, address: Registrar, 707 South Wood Street, Chicago 12, Illinois.

Spencer, Inc., of New Haven, Connecticut, introduces the Gordon-Barach support for patients with pulmonary emphysema. This abdominal support contains two spring metal bands that not only support the lower abdomen and increase the intra-abdominal pressure, but store mechanical energy during the inspiratory phase of respiration which is then employed during the expiratory cycle through recoil of the two spring bands.

The Argentine Society of Thoracic Surgery, sponsored by the Chair of Thoracic Surgery of the Faculty of Medical Sciences, University of Buenos Aires, will present the Second Argentine Congress of Thoracic Surgery August 17-20, 1954 in Buenos Aires. Persons who are interested may ask for preliminary programs, travel and hotel accommodations and registration from the "Secretaria del Congreso," Caseros 2153, Buenos Aires, Argentina.

The Cuban Chapter of the American College of Chest Physicians and the Commission of Medical Improvement of the National Medical College of Cuba will present a postgraduate course on diseases of the chest in Havana, June 7-11, 1954. The registration fee will be $30 and enrollment will be limited to 30 physicians. Further information may be obtained by writing to the registrar, Miss Olga Castaneda, Colegio Medico Nacional, G No. 506 Vedado, Havana, Cuba.

NOTICE

Effective with the January 1955 issue of
DISEASES OF THE CHEST (Volume XXVII)
the annual subscription rate will be increased from $12.50 to $15.00.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

20th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 17-20, 1954.

Third International Congress on Diseases of the Chest
American College of Chest Physicians
Council on International Affairs
Barcelona, Spain, October 4-8, 1954.

POSTGRADUATE COURSES

9th Annual Postgraduate Course on Diseases of the Chest
Hotel Knickerbocker, Chicago, Illinois, October 18-22, 1954.

7th Annual Postgraduate Course on Diseases of the Chest
Hotel New Yorker, New York City, November 8-12, 1954.

CHAPTER MEETING

Minnesota Chapter, Duluth, June 7.

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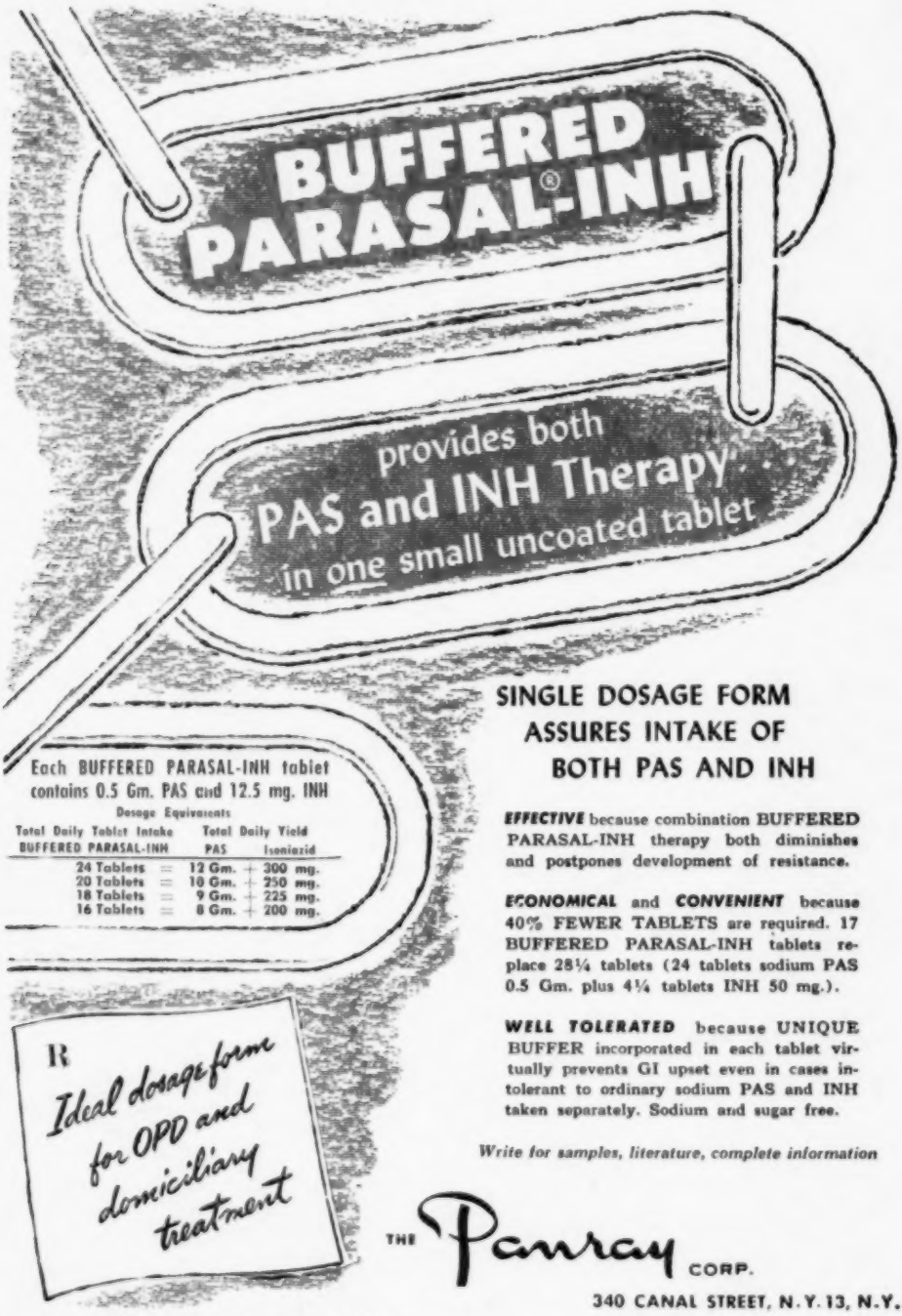

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